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THE JOURNAL OF CLINICAL ENDOCRINOLOGY

VOLUME 9 NUMBER 2

Next Annual Meeting, Haddon Hall, Atlantic City, June 3 and 4, 1949

FEBRUARY 1949

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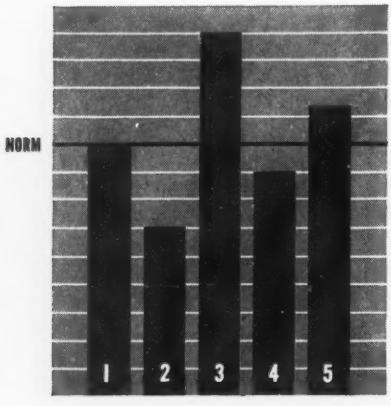

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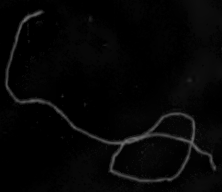

The Journal of
CLINICAL
ENDOCRINOLOGY

VOLUME 9 FEBRUARY, 1949 NUMBER 2
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TESTIS-PITUITARY INTERRELATIONSHIP

THE RELATIVE INABILITY OF TESTOSTERONE TO REDUCE URINARY GONADOTROPIN IN EUNUCHOID MEN

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From the Section on Endocrinology of the Cleveland Clinic and Frank E. Bunts Educational Institute

THE following is a report of studies made to compare the effectiveness of testosterone in therapeutic and greater than therapeutic doses with the effectiveness of estrogens, in lowering urinary gonadotropin levels. The subjects were men with severe eunuchoidism.

It is well recognized that high levels of follicle-stimulating hormone are present in the urine of men with testicular deficiency. In the patients studied here this feature has been considered an index of anterior pituitary hyperfunction. Experimentally testosterone has proved capable of preventing histologic as well as physiologic alterations in the pituitary gland of castrate male animals (1). Large doses have usually been employed for such studies. Some clinical evidence has been accumulated which indicates that similar results may, under certain circumstances, be demonstrated in man (2, 3).

The relative inefficiency of testosterone for inhibition of pituitary activity has been shown before. For example Hertz and Meyer demonstrated that in parabiotic rats doses as small as 0.2 gamma of estrone daily inhibit the male pituitary gland as efficiently as 15 gamma of testosterone propionate (4, 5). They also demonstrated that larger doses of androgenic substances are necessary to suppress the pituitary gland in male-female pairs than in female-female pairs. They concluded that the pituitary of the male

Received for publication, July 9, 1948.

rat was more difficult to suppress than that of the female. The ratio of the two hormones producing comparable effects in parabiotic animals is thus approximately 1 to 75. Catchpole, Hamilton, and Hubert (6) have reported a decrease of the urinary gonadotropin excretion to low levels in man following administration of testosterone propionate.

It has been our experience that in eunuchoid men doses of testosterone considerably greater than needed to overcome clinical evidence of androgen deficiency are necessary to lower the urinary F.S.H. (follicle-stimulating hormone) titer. In our patients the dose of stilbestrol which would lower urinary F.S.H. in eunuchoidism was between 0.5 and 1.5 mg. daily (3.5 to 10.0 mg. per week) and the effective dose of testosterone was in some cases 300 mg. or more per week. Thus our results yielded a ratio between 1:30 and 1:75 in man. Differences in methods of assay may be responsible for the diverse results reported in the literature. Several assays made in our laboratory using the method we employ and an extract made by the method of Freed and Hechter (7) which was used by Catchpole and Hamilton, yielded results much lower than those obtained by means of alcohol-precipitation extracts of the same pooled specimens. If unphysiologic doses of testosterone are necessary to suppress pituitary function to a normal level and physiologic doses fail to do so, a question arises concerning the mechanism by which this balance is normally attained. Is it due to a second testicular hormone (inhibin)? Could it be due to estrogen? It is of considerable interest that estrogens have a much greater power in this regard. On clinical grounds it seems to us somewhat unlikely that estrogens are normally responsible, since the dose found to be necessary to produce such a result in eunuchoid men is similar to the dose which is well known to produce such pronounced abnormalities as gynecomastia when used in men with prostatic cancer.

In the patients reported here testicular deficiency was diagnosed in each case on the basis of physical appearance and the presence of prostatic and genital atrophy and was corroborated by assays for 17-ketosteroids and urinary F.S.H.

Gonadotropin estimations performed in our laboratory on normal subjects by the method described by Klinefelter, Albright, and Griswold (8) yielded values ranging as high as 105 m.u. in twenty-four hours.

Urinary 17-ketosteroid assays were performed on neutral fractions by the MgO adsorption method (9), which, in a series of 48 of our normal male subjects, resulted in values ranging between 6 and 16 mg. per twenty-four hours. Normal levels for our laboratories are shown in the following table. They are given in more detail elsewhere (10).

Estimations performed on the urine of patients whose testes were de-

Normal Levels of Sex Hormone Excretion in Men

Assay	Daily range	Number of assays
17-KS	6–16 mg.	48
F.S.H.	26–105 mouse units	22

ficient showed an increase in the gonadotropin titer in all cases.

Figures 1 and 2 illustrate cases of severe eunuchoidism in which testosterone[1] absorbed from implanted pellets failed to decrease the titer of

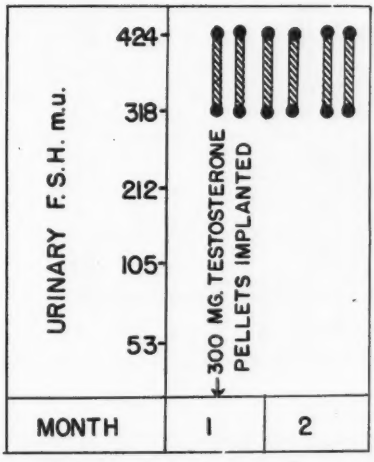

FIG. 1

urinary gonadotropins. In Figure 1, gonadotropin assay prior to implantation of 300 mg. of testosterone yielded a value of 318–424 m.u. in 24-hour specimens. Assays performed weekly for five weeks following the implantation failed to demonstrate any change of this level. In Figure 2, prior to the implantation of 600 mg. of testosterone the F.S.H. level was found to be greater than 105 m.u. on two occasions. The 17-ketosteroid level was estimated in the previous twenty-four hours and yielded a value of 5.9 mg.

[1] The testosterone used in these experiments was generously supplied by the Schering Corporation through the courtesy of Dr. Edward Henderson.

One month following implantation the gonadotropin titer remained unchanged, and the level was again found to be much more than 105 m.u. per twenty-four hours. A third patient with a pre-implantation urinary gonadotropin level of 318–424 m.u. per twenty-four hours was treated by implantation of 600 mg. of testosterone with no resultant depression of the gonadotropin titer according to tests done weekly for four succeeding weeks.

The failure of intramuscular injections of testosterone propionate and aqueous testicular extract to produce a fall in the urinary gonadotropin

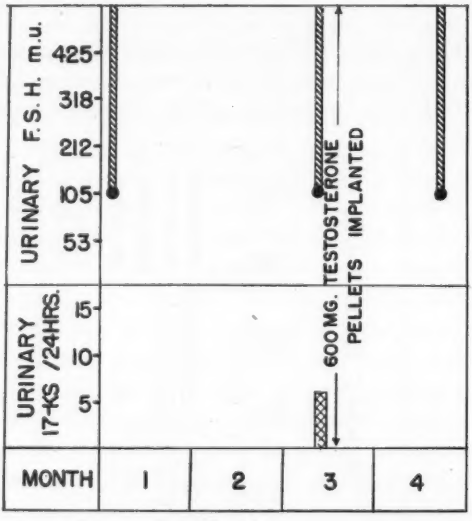

FIG. 2

level is illustrated in Figure 3. Here 100 mg. of testosterone propionate was given intramuscularly each week, and 2 cc. of aqueous testicular extract[2] was given by injection daily over the periods shown. Assays on three succeeding weeks following the initiation of this therapy yielded titers of 318–424 m.u. of F.S.H. per 24-hour specimen, and four weeks after beginning treatment the titer had risen to 424 m.u. per twenty-four hours. Following discontinuation of aqueous testicular extract the titer gradually fell to 212–318 m.u. per twenty-four hours.

All medication was discontinued for the following twenty-five days, and the titer again reached 424 m.u. per twenty-four hours. The patient was

[2] This aqueous testicular extract was virtually nonandrogenic and nonestrogenic. It was made from hog testes and obtained through the courtesy of The Upjohn Company, Kalamazoo, Michigan.

then given 3 cc. of aqueous testicular extract daily. In the succeeding three weeks gonadotropin titers remained unchanged, and one week prior to the cessation of aqueous testicular extract therapy, stilbestrol in doses of 1.5 mg. daily was prescribed. Four days later the gonadotropin level dropped

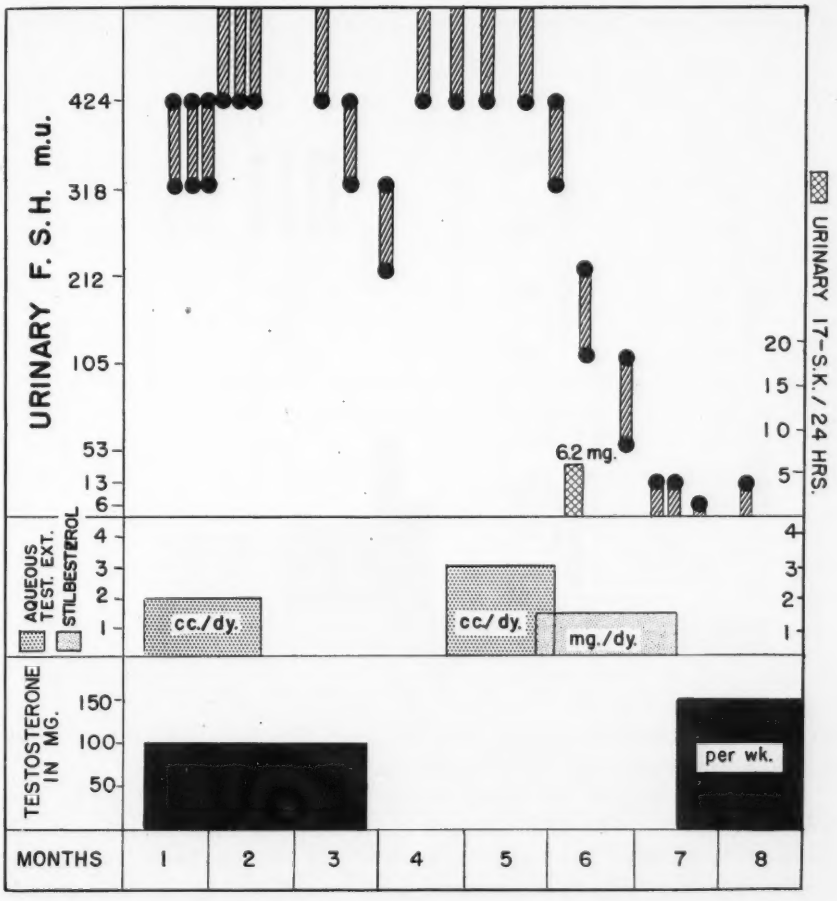

FIG. 3

to 318–424 m.u. One week later during stilbestrol therapy only, the 17-ketosteroid level was reported as 6.2 mg., and the F.S.H. titer gradually decreased, as illustrated in Figure 3, until normal and finally subnormal titers were obtained. Thus testosterone propionate in these doses in conjunction with aqueous testicular extract or the extract alone was shown to

have little effect on gonadotropin excretion. Stilbestrol, in contrast, exerted a pronounced effect on excretion of F.S.H. and presumably an inhibitory action on its pituitary production. The fact that the urinary gonadotropin level remained low for four weeks after cessation of stilbestrol therapy and during therapy with testosterone propionate in doses of 25 mg. six times

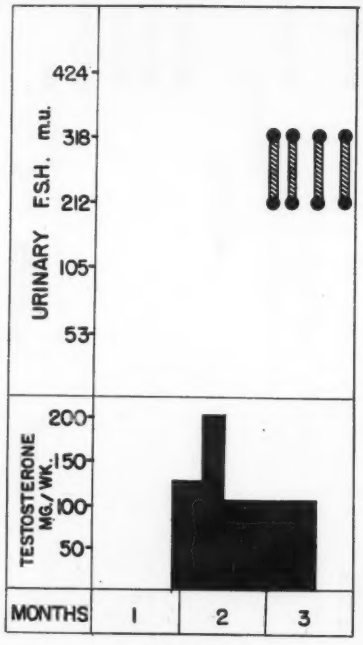

FIG. 4

weekly is, however, consistent with the belief that testosterone may exert a mildly inhibitory effect on the anterior pituitary.

Figure 4 illustrates the failure of the usual therapeutic doses of testosterone to effect the gonadotropin titer. Doses as high as 125 mg. per week for two weeks, 200 mg. for one week, and 100 mg. for five weeks, on repeated urinary F.S.H. estimation, were insufficient to depress gonadotropin excretion below 212 m.u. per twenty-four hours. In Figure 5, a dose of 300 mg. of testosterone propionate per week was used. Prior to the administration of the hormone the gonadotropin level was 212–318 m.u. and the 17-ketosteroid level was 4.7 mg.[3] Forty-six days after beginning

[3] This assay was made several weeks before the initiation of the above treatment while the patient was receiving intermittent therapy.

therapy with the large doses mentioned, the level was found to be 105–212 m.u. per twenty-four hours. Sixty-three days after institution of this therapy the gonadotropin level reached normal and was reported as 52–105 m.u. per twenty-four hours. Assay of the 17-ketosteroids at this time revealed the high titer of 21 mg. per twenty-four hours, twice the average normal in our laboratory and above normal range. All therapy

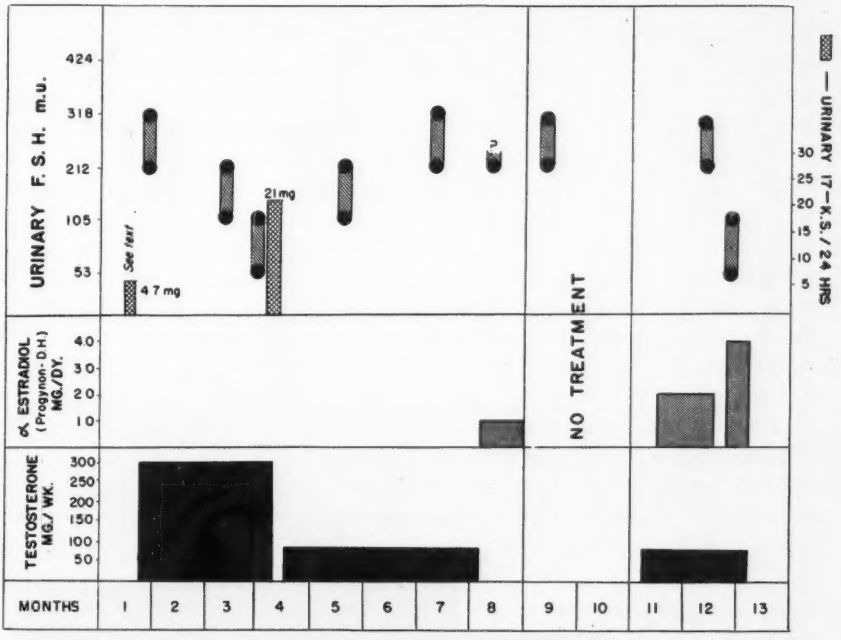

FIG. 5

was then discontinued for one week, and the patient was later given 75 mg. of testosterone propionate weekly. Under the smaller dosage the urinary gonadotropin levels gradually exceeded normal limits once again. These findings are in accord with results obtained by other investigators who demonstrated the depression effect of comparatively massive doses of testosterone on the pituitary gland in experimental castrated animals (11).

All hormonal therapy was discontinued. The patient was then given 0.5 mg. of estradiol orally daily. With this dosage the F.S.H. excretion remained above 212 m.u. per twenty-four hours after twenty-eight days of therapy. The patient then received no therapy for sixty-five days, after which time he again received 75 mg. of testosterone propionate per week.

Eleven days later this therapy was combined with 2 mg. of estradiol orally daily. Two weeks later the gonadotropin level remained 212–318 m.u. per twenty-four hours. Twenty-four days after beginning this treatment the gonadotropin level reached a normal value. Once again the inhibitory action of estrogen upon the anterior pituitary was demonstrated and may

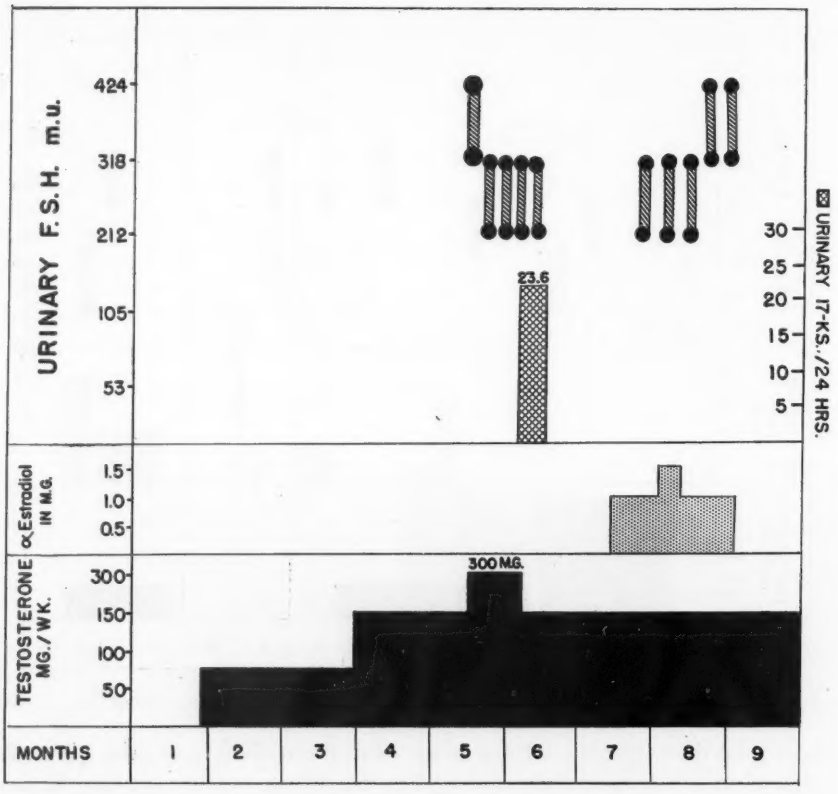

FIG. 6

be compared with similar effects obtained with testosterone in more than physiologic doses.

In Figure 6 an instance is shown in which increased doses of testosterone propionate over a period of twelve weeks, culminating in doses of 300 mg. for three weeks, succeeded in depressing the gonadotropin titer slightly. The 17-ketosteriod level at this time was reported as 23.6 mg. per twenty-four hours. The dose of testosterone propionate was then reduced to 150

mg. per week and estradiol in a dose of 1 mg. orally daily was prescribed and later increased to 1.5 mg. orally daily. This did not alter the titer of urinary gonadotropins and gradually the level rose to over 424 m.u. per 24-hour specimen.

In Figure 7 the same severely eunuchoid individual referred to in Figure 6 was given estrogenic substance, having received at least 150 mg. of testosterone propionate per week in the preceding five months. The testosterone propionate and, in addition, aqueous testicular extract in doses as high as 4 cc. per day were incapable of reducing the gonadotropin titer, as evidenced by repeated assays. Stilbestrol was then begun in doses of 0.5 mg. daily with no effect on the F.S.H. level. The 17-ketosteroid level was 13.8 mg., and the gonadotropin titer was reported as over 424 m.u. per twenty-four hours. After seven weeks of therapy the dosage of stilbestrol was increased to 1.5 mg. orally daily, with resultant depression of the F.S.H. titer to 318–424 m.u. per twenty-four hours. Thereupon the dosage of stilbestrol was increased to 2.0 mg. orally daily and the testosterone propionate reduced to 150 mg. per week. During this therapy a greater depression of the gonadotropin level occurred, resulting in normal values. This level was maintained as long as the estrogen was given in this dosage. Reduction in estrogen intake was followed by a gradual elevation of the F.S.H. level, and discontinuation of estrogen therapy resulted in a rise to the original titer of over 424 m.u. per twenty-four hour specimen. After a period of two months during which no therapy was given, the patient was given 100 mg. of testosterone propionate weekly and, in addition received 2 mg. of estrololactone daily. After five weeks of this therapy no noticeable effect was produced, and the gonadotropin excretion remained over 424 m.u. per twenty-four hours.

In Figure 8 are demonstrated the urinary gonadotropin and 17-ketosteroid levels in a eunuchoid individual in whom dosage of 75 mg. of testosterone propionate per week for almost two years had produced a pronounced increase in masculinization. Under this regimen the gonadotropin level still exceeded 212 m.u. per twenty-four hours, and the 17-ketosteroid level was reported as 9.3 mg. per twenty-four hour specimen. An increase in the dose of testosterone propionate to 150 mg. per week for nine weeks resulted in urinary gonadotropin titers of 105–212 m.u. Further increase in the dose of testosterone propionate to 300 mg. per week elevated the 17-ketosteroid level to 12.9 mg. per twenty-four hours but did not alter the F.S.H. level. Stilbestrol in doses of 0.5 mg. daily depressed the gonadotropin level to normal within two weeks. Upon cessation of therapy the titer of urinary gonadotropins gradually increased to the original level of over 424 m.u. per twenty-four hour specimen.

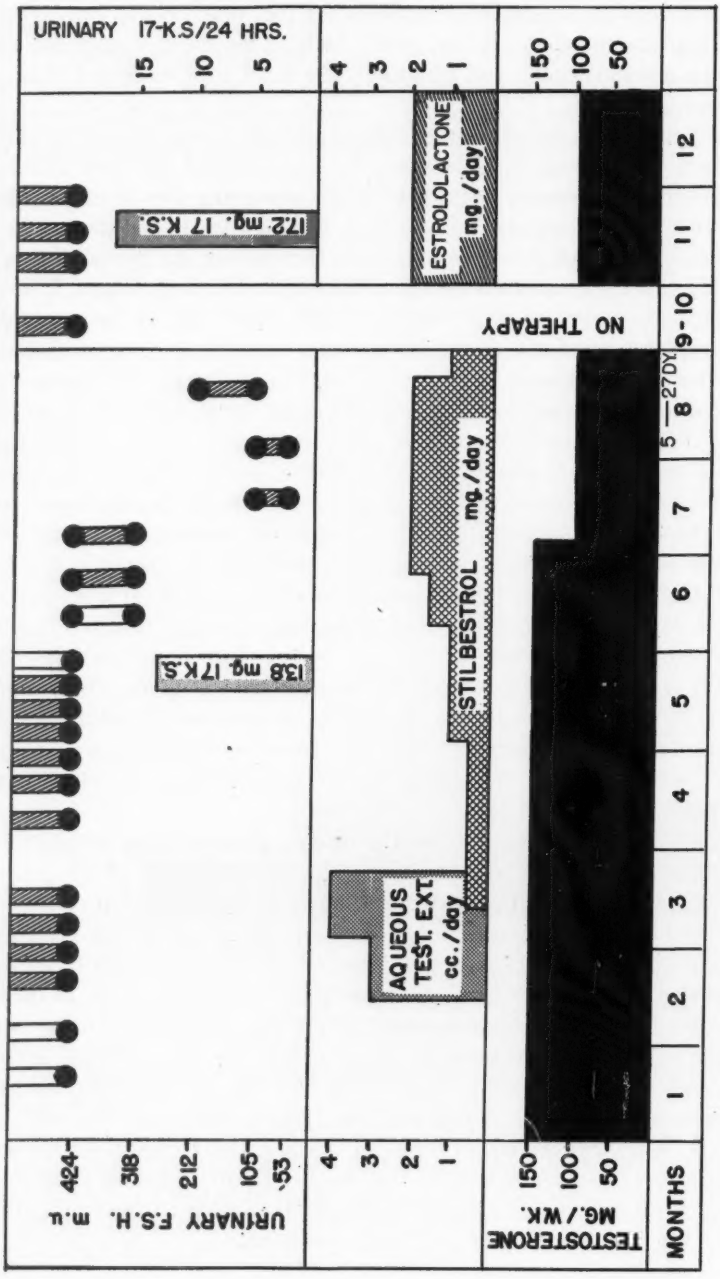
INABILITY OF TESTOSTERONE TO INHIBIT PITUITARY
URINARY F.S.H. m.u.
424
318
212
105
53
138 mg. 17 K.S.
URINARY 17-K.S/24 HRS.
15
10
5
17.2 mg. 17 K.S.
4
3
2
1
AQUEOUS TEST. EXT cc./day
STILBESTROL mg./day
ESTROLOLACTONE mg./day
150
100
50
TESTOSTERONE MG./WK.
NO THERAPY
MONTHS
1
2
3
4
5
6
7
5 — 27DY 8
9-10
11
12

FIG. 7

In the above cases we have demonstrated the relative lack of effect of testosterone on the urinary titer of follicle-stimulating hormone of the anterior pituitary in the urine of patients suffering with testicular deficiency. In the cases illustrated, the use of testosterone in amounts sufficient to

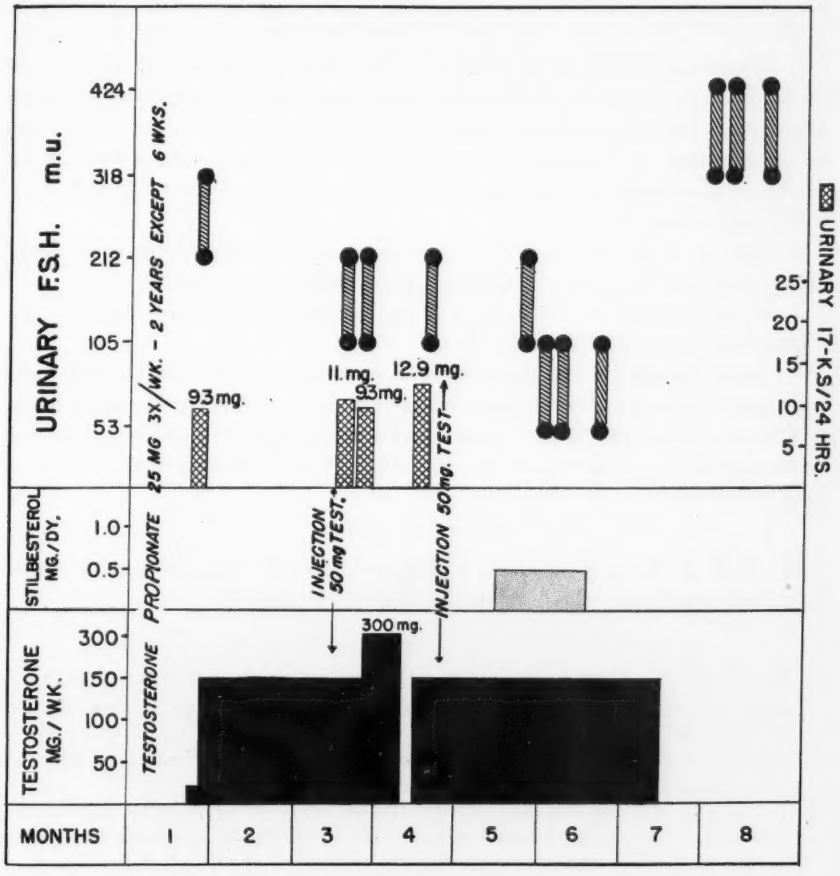

FIG. 8

raise the titer of 17-ketosteroids to normal range asserted little or no effect on the F.S.H. titer. Some influence is shown when large doses were employed. The graphs also demonstrate that estrogens in doses approximating those in common clinical use do lower the urinary F.S.H. in patients with testicular failure.

Although a lack of utilization has been postulated as the reason for high titers of gonadotropins in the urine of eunuchoid men, the reverse could scarcely be an explanation for the lower levels of these substances under the circumstances cited above. In these instances pituitary suppression would appear a more logical explanation.

CONCLUSIONS

1. In cases of severe hypogonadism in the male, urinary F.S.H. titers were not reduced to normal levels by administration of testosterone in the usual therapeutic form and dosage, and in amounts sufficient to create normal titers of urinary 17-ketosteroids and clinical signs of masculinization. Very large doses of testosterone apparently do have this power, as has been previously claimed.

2. Stilbestrol when employed in ordinary therapeutic doses does lower the urinary F.S.H. titer in primary hypogonadism in men.

3. Estrololactone in doses of 2.0 mg. per day failed to lower urinary gonadotropins in one patient.

4. Testosterone in the doses employed here is adequate to overcome androgen deficiency, but fails to inhibit pituitary activity. These facts are consistent with the theory that a second testicular hormone (inhibin) exists normally, and that it has a pituitary-inhibiting power similar to that of estrogen.

Acknowledgment

We wish to thank Miss D. C. Tweed and Miss B. J. Sipher for the careful technical assistance which made these studies possible.

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THE TREATMENT OF ACROMEGALY

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THE development of bony and tissue changes in patients with acromegaly is so insidious that the victims of this disorder as a rule seek medical assistance only in its advanced stages. Very little can then be accomplished in the correction of these effects.

On the other hand, satisfactory treatment of acromegaly is usually possible providing the condition is recognized early, and if energetic attempts are made to follow patients with this malady at regular intervals. The unpredictable course of acromegaly, however, renders evaluation of treatment difficult in some cases. This review of our experience in the management of acromegaly was undertaken to evaluate past treatment with the hope of possible improvement in the future.

The first objective of treatment is the relief of symptoms resulting from the expanding tumor, if such exists, which may cause headache and visual or other neurologic disturbances. Many patients with acromegaly are not affected in this way, so that the question of treatment of secondary hormonal signs or symptoms must be investigated. Occasionally an enlarged sella is found on roentgenologic studies of an individual without obvious acromegaly and lacking symptoms or evidence of pressure effects, and in whom there is no evidence of hormonal change even after exhaustive analyses. Since early treatment of this condition is important, such cases must be included as subjects for therapy whenever any change indicative of expanding tumor or increased hormonal activity becomes apparent. At this time as well as on first examination we are confronted with the problem of demonstrating active acromegaly or hyperpituitarism. Signs or symptoms of increased local pressure from the tumor do not necessarily mean hormonal overactivity, but an attempt should be made to relieve pressure regardless of the question of progressive acromegaly. Amenorrhea in the female and impotence in the male may usually be considered secondary effects due to pressure, since these symptoms occur chiefly after considerable enlargement of the sella. These dysfunctions are sufficient to warrant conservative therapy, namely radiation.

If all evidence of intracranial and intrasellar pressure is absent, how can one be sure that hyperactivity is nonexistent? The presence of acromegalic

Received for publication July 24, 1948.

changes, *i.e.*, prognathism, coarsened facial features, enlargement of the tongue, hands and feet, does not indicate activity at the time of the initial examination, and since these findings develop so insidiously, months of observation may be necessary to establish the presence of hypersecretion of the pituitary growth factor. Two other hormonal effects are subject to clinical appraisal; namely, the thyrotropic and the diabetogenic factors. The first usually causes enlargement of the thyroid and an elevated basal metabolic rate together with clinical hyperthyroidism. Active diabetes, particularly of recent origin, is often considered evidence of excess pituitary secretion, yet it is our impression that either or both of these hormonal complications may be present without concomitant progressive enlargement of the acral parts. Explanation of the first phenomenon might be found in the catabolic nature of hyperthyroidism offsetting the anabolic nature of early active acromegaly; and in the second instance, as suggested by Young (1), diabetes may be the result of exhaustion of the islets of Langerhans following prolonged overstimulation.

Reifenstein (2) *et al.* have suggested that the level of blood phosphorus, because of its elevation during the active growth period in a normal individual, may be used as an index of growth hormone in acromegaly. These authors apparently consider 3.2 mg. per 100 cc. as the average normal value. In observations on 19 cases, 4 of which were from this series, we obtained values as shown in Table 1. There appears to be a lowering in these cases after roentgen therapy. Persistent values over 4.5 mg. per 100 cc. point to increased growth activity, but we believe that too much emphasis should not be placed on single estimations, especially between values of 4 to 4.5 mg. per 100 cc., because of the possible inherent error in the analysis when carried out in routine clinical laboratories. Specimens should be taken during fasting, since food tends to lower blood phosphorus.

The term "fugitive" acromegaly, used by the late Dr. Cushing, is in itself a fugitive term and unless the individual in question has an enlargement of the sella or some other stigmata of previous pituitary hyperactivity, such a diagnosis is largely conjecture. The condition is most frequently seen in cases of chromophobe or mixed pituitary tumor. Sosman has pointed out that cases of chromophobe tumor may have a brief period of pituitary hyperactivity with slight acromegalic changes, followed soon by the classical chromophobe signs and symptoms.

In young females, when evidence of pressure is lacking and when there are in the face and extremities early tissue changes which may be partially reversible together with a minimum of irreversible bony enlargement, early therapy is justified even without the usual clear-cut evidence of hyperactivity. In these cases particularly, a persistently high blood phosphorus should be helpful.

TABLE 1. BLOOD PHOSPHORUS DETERMINATIONS IN ACROMEGALY

Serum phosphorus, mg. per 100 cc.					
Considered active clinically			Considered inactive clinically		
Case No.	Before treatment	After treatment†	Case No.	Before treatment	After treatment
1	5.1	4.2	13		3.4*
	5.5		14	3.9	4.0
2	5.0	4.5	15	4.4	
	4.7	4.4	16		3.2**
		3.7	17		3.8**
3	5.0	4.1			3.2
	4.1	3.2	18		3.1#
4	4.4		19		4.3
	3.5				
5	4.5	3.5**			
6	4.1				
7	4.0				
8	4.1				
9	4.2	4.1			
	4.1	3.5			
10	5.1	4.7§			
	4.9	3.9			
		4.1			
11	4.4	3.1			
12	4.4	2.8			

Average before initial treatment, active cases, 4.52.

Average after initial treatment, active cases, 3.9.

Average, inactive cases, 3.5.

† Treatment usually consisted of one course of x-ray therapy between first and second figures. Subsequent figures listed under "Before treatment" show values before second course, in patients still being treated.

* "Burned out." No treatment.

** After surgery and x-ray treatment.

After x-ray treatment.

§ We are indebted to Dr. Anna Forbes of the Massachusetts General Hospital for some of these analyses in this case.

One must rely upon the history in some patients to establish early acromegalic effects since prognathism may not be detectable; but if suspected, enlargement of the hands and feet must also be present to render questionable prognathism of significance. Radiation therapy, in these cases, too, is the logical treatment for at least six months or a year unless there is in-

creasing impairment of the visual fields. During this time an attempt may be made to find evidence of progression by careful comparative measurements of the sella turcica, photographs, roentgenograms or plaster replicas of the face and hands. The volume of water displaced by hands was used many years ago by Falta (3) for estimating tissue changes. In young females it is desirable, if not imperative, to preserve normal facial features, and surgical removal of the tumor should be seriously considered as the most logical therapy if no other contraindications exist. It must be remembered, however, that surgical removal of the tumor is not always satisfactory and carries a certain risk. While it may thwart acromegaly, there is no positive assurance that the adenoma will not recur because of technical difficulties in its enucleation. Furthermore, if a young acromegalic female is menstruating regularly and wishes children, either radiation or surgical treatment might be followed by amenorrhea, although we have not seen this happen after either form of therapy in such cases. Both types of treatment may restore normal menstruation (and ovulation?) in the amenorrheic, acromegalic patient, but there is a possibility of permanent cessation of the catamenia after surgical removal of the adenoma. The decision as to which course to pursue in such cases is difficult, but the safer certainly is roentgen therapy, if any treatment at all seems warranted before conception.

Objectives of treatment in acromegaly may be summarized as follows:

A. Relief of pressure and its effects

1. Relief from local pressure symptoms on adjacent structures
   a. Headaches.
   b. Visual disturbances (*i.e.*, field defects and impaired acuity).
   c. Prevention of extension of growth into the sphenoid sinuses or above the sella intracranially, and possibly recession of invasion in these areas.
   d. Mental or neurologic changes, such as convulsions, hemiplegias and psychoses.
2. Relief from pressure within the sella by the tumor on normal pituitary tissue or on the neurohypophysis.
   a. Amenorrhea in the female.
   b. Impotence in the male.

B. Relief of hyperhormonal effects

1. Prevention of further bone changes or diminution of tissue effects of acromegaly with possible restoration to normal in early cases.
2. Relief of headaches (which may be of hormonal origin).
3. Relief of hyperthyroidism.

4. Control of diabetes.
5. Decrease in cardiovascular symptoms, such as hypertension or congestive heart failure.
6. Relief of symptoms from bone damage, such as hypertrophic arthritis, exostoses, kyphosis or other orthopedic complications; and perhaps prevention of these progressive conditions.

C. Relief of late or concomitant hypohormonal effects

ROENTGEN DIAGNOSIS

The roentgen diagnosis of chromophil tumors is dependent upon the findings in the cranial vault, and the most important change is the direct pressure effect upon the sella turcica. In a tumor arising within the sella itself and held in check superiorly by the capsule, there is a gradual ballooning of the sella, producing thinning of the bony wall, depression of the floor into the sphenoid sinuses, dorsal displacement of the dorsal clinoids associated with thinning and occasionally fracture, or complete absorption. The anterior clinoids may be pushed farther apart than normal. Unilateral enlargement is not uncommon. The size of the sella varies in normal individuals and it is necessary, therefore, to establish its limits arbitrarily; thus, a tumor may be of considerable size, having produced bone and soft tissue changes, before the sella becomes enlarged beyond the upper limits of normal. We believe a sella turcica 12 mm. deep by 15 mm. wide is a satisfactory standard for the upper limits of normal, and 22 to 26 mm. as the normal dimension for the distance between the anterior clinoids when measured in the postero-anterior view.

For some time we have been using the lateral contour area, as measured in square millimeters on transparent ruled paper, after the method of Haas, (4), for successive serial comparisons of sellar size. We believe this probably provides a more accurate method than using depth and width measurements of the sella turcica for such purposes. The average area of the lateral contour is approximately 74 sq. mm. with a normal range of from 70 to 130 sq. mm. Values of 130 to 150 sq. mm. may be considered borderline. In the presence of other findings, such as thinning of the floor of the sella, and enlargement of the accessory sinuses or prognathism, the diagnosis should be suggested regardless of the size of the pituitary fossa.

CLINICAL MATERIALS AND METHODS

Twenty-nine patients with acromegaly were seen at the Lahey Clinic from 1932 to 1945 (Tables 2 to 5). Clinical data on these cases for the most part have been described elsewhere (5). Of the 29 patients, 1 was untraced, 7 were reached by mail, and 6 are dead. Of these, 20 patients re-

ceived at the Clinic either radiation or radiation and surgical treatment directed toward the pituitary itself, as follows: surgical removal of the pituitary tumor, 5 cases (followed by radiation in 2 cases); surgical exploration without removal of tumor, 1 case; and roentgen therapy without surgical removal of the adenoma, 14 cases. Three other patients in this series received radiation therapy elsewhere. In addition, other therapeutic procedures of importance were: subtotal thyroidectomy, 2 cases; thiouracil for hyperthyroidism followed by subtotal thyroidectomy, 1 case; removal of osteoma of the orbit, 1 case; treatment to relieve pain of dorsal kyphosis, 2 cases; and for pain of hypertrophic and mild arthritis, 2 cases; stilbestrol administration in an attempt to relieve headache and hot flashes, 2 cases; for persistent lactation, 1 case; and for amenorrhea, 1 case.

Method for Radiation Therapy

Radiation is generally considered the method of choice in the treatment of chromophil pituitary adenomas producing acromegaly (6) (Table 2). Marked visual-field defects are not frequent in this disorder so that in most instances radiation is used in cases of headache and to decrease the size of the tumor in an attempt to relieve the compressed portions of the normal gland and thus permit it to function again, as well as to decrease the hormonal secretion of the tumor itself.

No uniform plan of roentgen dosage was employed; treatment was given empirically when deemed necessary because of symptoms. A review of the therapeutic results in this group shows that those who received larger doses of irradiation have had, as a rule, greater and more lasting relief. The lethal dose for this tumor is not known, and no patient has received sufficient radiation to produce clinical evidence of brain or bone damage and no severe skin changes have thus far developed.

The present plan of radiation therapy is to direct the beam through two lateral portals using 200 k.v.p., 20 ma., 50 cm. distance, 1 mm. of copper plus 1 mm. of aluminum, HVL 3.7 mm. copper, giving 300 to 400 r (measured in air) daily through a 5 cm. portal, treating one portal daily, with the x-ray beam directed through the temporal region toward the sella turcica. A series of ten treatments with the total dose of 2000 r to each temporal region, is given. The approximate tumor dose delivered to the pituitary was 50 per cent of the air dose or a total tumor dose of 2000 r delivered to the tumor. This may be repeated eight weeks later, although if the tumor is radiosensitive an initial series of ten treatments should be large enough to produce good palliative results. If relief is not attained by this amount of therapy, it may be because the lesion is radioresistant and possibly cystic. It is fair to assume, however, that more persistent pal-

TABLE 2. ACROMEGALY TREATED BY ROENTGEN RAYS

Case, No., age (yrs.) and sex	Duration of disease	Duration of observation	Degree of acromegaly	Headache	Headache relieved	Amenorrhea	Amenorrhea relieved	Visual field defect	Visual field defect relieved	Roentgen ray therapy. No. of treatments	Duration of roentgen ray therapy	Duration of follow-up since last treatment
1 27 M	5 yrs.	14 yrs.	III	+	+	−	−	0	−	1930–8 1932–8 1934–6 1943–10	13 yrs.	1 yr
2 36 M	8 yrs.	8 yrs.	II	+	+	−	−	0	−	13	2 yrs.	8 yrs.
3 30 F	1 yr.	7 yrs.	II	+	+ 0	0	−		−	42	6 yrs.	1 yr.
4 50 F	10 yrs.	4 yrs.	I	+	+	−	−	+	+	26	2 yrs.	—
5 43 F	2 yrs.	7 yrs.	I	0	−	0	−	0	−	2	2 days	None
6 48 F	9 yrs.	6 yrs.	II	+	+	−	−		−	24	3 yrs.	4 yrs.
7 20 M	5 yrs.	3 yrs.	II	0	0	0	0	Appeared 1 yr. after first visit			2 yrs.	Under treatment.
8 32 F	2 yrs.	5 yrs.	I	+	0	+	0	0	0	36	4 yrs.	1 yr.
9 46 F	6 yrs.	5 yrs.	II	+	+	+	+	0	−	24	6 mos.	18 mos. 36 mos.
10 32 F	2 yrs.	16 mos.	I	0	0	+	+	0	−	12	1 yr.	9 mos.
11 41 F	4–12 yrs.	11 yrs.	II	+	0	+	0	0	−	9	6 mos.	10 yrs.
12 40 M	10–18 yrs.	+	II	+	+	−	−	0	−	12	6 mos.	3 yrs.
13 37 F	6 yrs.	1 yr.		+	+	Excess and irregular	Became regular	0	−	10	6 mos.	None after last x-ray treatment
14 37 M	5 yrs.	3 mos.	IV	0	0	0	0	++	++	12	3 mos.	Under treatment

liation may be obtained by further treatment, a course we are now pursuing.

It is customary, following the plan of Sosman, to give irradiation usually within the first month, to all postoperative cases. This treatment consists of the same factors as previously outlined.

TABLE 2—(*continued*)

Sella; size before treatment (mm.)	Sella, size after treatment (mm).	Other data	Other treatment	Comment
16×19 (1930)	15×21 14×19 (1944)	Tinnitus	None	No progress in acromegaly. Some changes in temperament. Libido excessive. General condition good.
28×35	21×35	Protrusion of tumor into nasopharynx		Complete erosion of sphenoid sinus and protrusion into nasopharynx. Receded completely after x-ray therapy Tissue regression noted. No symptoms of progression of acromegaly. Considered stationary.
14×17	13×15 ? well formed		One testosterone pellet	No advance in acromegaly. Temporary relief of headache after x-ray therapy. Amenorrhea after first series of x-ray treatment proved to be due to pregnancy. Delivered normal child without incident.
21×26		BMR +43; diabetes	40-0-15 units of insulin	Natural menopause. Headaches and visual field defects relieved. BMR fell to +7. Died in diabetic coma after stopping insulin. Tissue regression noted.
17×12 (1936)	19×14 (1943)	BMR +20; goiter	Subtotal thyroidectomy in 1936	Operated on for goiter in 1936 at which time acromegaly was recognized. Sella was not enlarged. Seen again in 1943. Sella enlarged. Patient became psychotic after 2 x-ray treatments. Died in state hospital of acute infection in 1943.
14×15	11×13		Benzedrine, stilbestrol 5 mg. weekly	Natural menopause at 42. Relief of headache for 4 yrs.; recurred. Fatigue came on after x-ray therapy. No help from stilbestrol 5 mg. parenterally weekly. No progress in acromegaly.
R15×23 L22×33	R22×25 L30×34 (See Figs. 1 and 2)	Severe acne	Estrone sulfate or stilbestrol up to 15 mg. daily	Acromegalic gigantism; reduced libido. Testes somewhat atrophic. No progress of acromegaly for 2 yrs., then reduced vision and enlarged sella. Surgery in 1946.
20×21	21×22 23×25	Persistent lactation	Stilbestrol, 5 mg. weekly	Onset of acromegaly after pregnancy. No relief of headache or slowing of lactation with x-ray. Some increase in acromegaly. Temporary relief of headaches and lactation with stilbestrol. Increasing size of sella.
15×16	15×18 14×18		Stilbestrol, orally, 0.5 mg. daily	Unilateral enlargement of sella. Improvement in headaches but not complete. Periods returned, but irregular. Hot flashes controlled by stilbestrol.
10×15	12×15			No progress in acromegaly. Improvement in acne. Periods returned.
2 times normal				Headaches persist. No other change. Degree of acromegaly not known but patient writes "condition same."
21×22	19×22	Marked hyperthyroidism; goiter	Iodine; thiouracil	Marked sweating, tremor, tachycardia. BMR +70. No help with x-ray or iodine. BMR +11 on thiouracil. Subtotal thyroidectomy; good result for 3 years, then recurrence.
Films lost				X-ray treatment seemed to stop progress which had been steady for six years. Some tissue regression noted. Excessive flow stopped, as did much of headache. No follow-up after last x-ray treatment. Epileptic attacks (several) which did not recur for 1 yr. after treatment.
20×22 Depressed into sphenoid		Obliteration of oral pharynx by tongue		Chronic exhaustion; excessive drowsiness. Thyroid normal; BMR +5. Positive glucose tolerance curve. Response to 12×300 r. Excellent symptomatic relief.

RESULTS

RADIATION THERAPY

1. Tissue changes

As a result of radiation, regression of the enlarged soft tissues may take

TABLE 3. ACROMEGALY TREATED BY SURGERY AND IRRADIATION
(up to 1945)

Case, No., age (yrs.) and sex	Duration of disease on admission	Duration of observation	Degree of acromegaly	Headache	Headache relieved	Amenorrhea	Amenorrhea relieved	Visual field defect	Visual field defect relieved	Surgery of tumor	Other surgery	X-ray therapy. No. of treatments	Duration of x-ray therapy	Duration of follow-up since last therapy
15 35 F	8 yrs.	6 yrs.	II	0		+	+	0	–	1932 1937 1940	0	40	2 yrs.	———
16 30 M	3 yrs.	9 mos.	II	++	0	–	–	Slight edema	–	Not removed; explored	0	2 series	3 mos.	3 mos.
17 23 F	11 mos.	1 yr.	I	+	+	+	0	++	+	Yes	0	6 p.o.	p.o. 1 wk.	12 mos. 40 mos.
18 28 F	3 yrs.	15 mos.	II	++	+	+	0	0	0	Yes	0	12 p.o.	3 mos.	18 mos.
19 33 F	8 yrs.	5 yrs.	II	+	0	+	+	?	0	Yes	0	18 before op. 6 after op.	6 mos.	24 mos.
20 48 F	5 yrs.	1 yr.	III	+	+	+	0	++	+	Yes		7 before op. 8 after op.	2 mos.	9 mos.

place. These changes are often noted by the patient; namely, that the tongue feels and becomes smaller, and the flesh of the hands, particularly of the palms becomes more pliable. These results can be expected in four to eight weeks following radiation. Attempts to demonstrate this change by photographs and plaster casts as yet have not been satisfactory, but it should be possible to illustrate tissue regression in some cases; however, these procedures have not been used extensively. As far as we have been able to tell, only 2 of our treated patients have shown any noticeable progress in the enlargement of the acral parts after treatment was begun (Cases 7 and 8).

2. Visual changes

In one case visual field defects were completely eliminated following radiation. Improvement of visual acuity was observed in another patient with generally restricted fields. Two other patients were thought to have slight improvement in minor visual field changes, but this was equivocal. Marked improvement in visual field defects occurred in two other patients but both have been subsequently operated upon (1946), one because of a sudden hemorrhage within the adenoma some months after the last course of radiation (Case 20), with great visual impairment, and the other,

TABLE 3—(*continued*)

Pathologic report of tumor	Sella; size (mm.)	Sella; size after treatment (mm.)	Other data	Results of treatment
Mixed, acidophilic predominantly			X-ray therapy before surgery failed to relieve. Associated attacks of unconsciousness; mental upsets.	Much improved by first operation 1932. Second operation helped—extensive recurrence. Third operation performed elsewhere when patient was moribund. Dead.
	Enlarged	?		X-ray therapy did not help headache. Died 9 mos. later of leukemia. Blood examination before treatment gave normal results.
Mixed, with hemorrhage	18×19	15×19 to 19×20	Stilbestrol orally for six months, 0.5 mg. daily	No progression of acromegaly. Still amenorrheic and complains of fatigue. Good tissue regression. Recurrence 42 months later; larger sella. Controlled by x-ray.
Specimen deteriorated	17×20	16×17 1 yr. recalcification	Hyperthyroidism present. BMR +44	No progress of acromegaly. Gain of 50 pounds. Hyperthyroidism improved. Good tissue regression.
Eosinophilic	14×21	15×20	Received stilbestrol propionate 5 mg. weekly for several months with no help.	18 x-ray treatments given in period of 6 mos. failed to relieve headache or amenorrhea permanently. Tumor progressed in size in 2 yr. period following. No progress in acromegaly. Surgery caused tissue regression, and relief of amenorrhea. Headaches continue but less severe.
Unclassified	20×11	21×10	Amenorrhea due to hysterectomy	Halved vision in one eye before irradiation, improving at first on x-ray therapy, then sudden, rapid progression. Complete restoration of visual fields following surgery.

because of an enlarging sella and decreasing vision in spite of radiation (Case 7)—*see* section on treatment with estrogens (Figs. 1 and 3).

3. Changes in the size of the sella turcica (Table 5)

In 14 cases we were able to make roentgenograms of the skull from time to time, and the following observations were made. In one case (Case 5) in which the diagnosis of acromegaly was made in 1936, a subtotal thyroidectomy was successfully performed because of hyperthyroidism. At that time the sella was not considered to be enlarged. The patient returned seven years later because of headache. The sella had increased from 17 by 12 mm. to 19 by 14 mm. Two roentgen treatments were followed by acute psychosis. This patient was transferred to a mental hospital where she died subsequently of pneumonia, never having recovered from her psychotic state. She should have returned for periodic examination, since earlier radiation therapy might well have prevented the expanding tumor and probably the psychosis. In another acromegalic (Case 7; Figs. 2 and 3), no progressive enlargement was detected during the first year of observation, but it rapidly developed in the second year. No treatment was given in this case until visual field defects as well as a change in the acromegaly was noted. In 4 other cases in which inadequate therapy was given

TABLE 4. PATIENTS WITH ACROMEGALY IN WHOM THE PITUITARY WAS NOT TREATED AT THIS CLINIC

Case No., age (yrs.) and sex	Duration of disease	Duration of observation (up to 1945)	Degree of acromegaly	Headache	Headache relieved	Amenorrhea	Return of catamenia	Visual field defect	Surgery	Size of sella (mm.)	Other data	Comment
21 34 F	8 yrs.	6 yrs.	II		+			0	Subtotal thyroidectomy. BMR +55	18×18; enlarged; depressed into sphenoid sinus	Marked hypertrophic arthritis with dorsal kyphosis	Good result from operation. Back deformity still disabling. No x-ray treatment; lives too far away. Not known if acromegaly progressed. Follow-up during first year.
22 58 M	Long time	2 mos.	III	?	–	–	–	0	BMR +57	Enlarged; clinoids separated 14×24	Destructive lesion of D6 and D7. Hypertrophic arthritis marked.	Transferred elsewhere; died of subacute bacterial endocarditis. Thyroid moderately enlarged. No response to iodine clinically.
23 40 M	25 yrs.	6 mos.	II	0	–	–	–	0	Removal of osteoma of orbit 3.4×4.5	19×20	Incomplete fusion right hip	Successful removal of osteoma of orbit which produced protrusion of left eye.
24 41 F	11 yrs.	7 yrs.	III	?	–	+	0	Slight temporal defect	Radical left maxillary sinus operation	Enlarged sella eroded down to sphenoid sinus	Cervical, dorsal kyphosis	Marked increase of acromegaly according to patient (letter). No other treatment carried out. Patient lived in northern Canada. Not possible to be treated at home.
25 63 M	?	1 exam.	II	0	0	–	–	0	0	Enlarged, 15×21		No complaints. Unaware of condition.
26 50 M	5 yrs.	11 yrs.	I	0	–	–	–	0	0	Moderate, 13×13	Paranoia; coronary sclerosis; hypertrophic arthritis	Patient died in 1944.
27 20 F	2 yrs.	1 visit	II	?	+	?	–	Constricted fields, 2–3 diopters; edema	0	Enlarged; erosion of clinoids		X-ray advised. Treated elsewhere; no follow-up. Shoes changed from 5½ to 7½, then remained stationary.
28 47 F	3 yrs.	8 yrs.	I	+	0	0	–	0	0	Enlarged; floor depressed		X-ray; 13 treatments elsewhere. Follow-up says "continued headache." Afraid to have more treatment. Wears half size larger shoes. High blood pressure.
29 29 F	4 yrs.	+	II	0	–	+	–	0	0	6×9	Diabetes	X-ray begun elsewhere. Headaches relieved with x-ray. Not observed long enough for conclusions. Diabetes mellitus.

TABLE 5. CHANGES IN SIZE OF SELLA TURCICA FOLLOWING RADIATION THERAPY

	Measurements in millimeters	Measurements in square millimeters	Period of time between measurements	Number of treatments* between measurements
Decrease in size				
Case 1	16×19 to 14×19	267 to 161	13 yrs.	32
Case 2	28×35 to 21×35	1020 to 601	2 yrs.	13
Case 3	14×17 to 13×15	211 to 184	6 yrs.	42
Case 6	14×15 to 11×13	210 to 168	3 yrs.	24
Case 12	21×22 to 19×22	448 to 388	4 yrs.	12
Case 17	18×19 to 15×19 to 19×20	285 to 252	1½ yrs.	6 (postop.)
Case 18	17×20 to 16×17	360 to 329	16 mos.	12 (postop.)
Case 20	20×11 to 21×10	178 to 161	5 mos.	7 (preop.) 8 (postop.)
Increase in size				
Case 5	17×12 to 19×14		7 yrs.	2
Case 8	20×21 to 21×22 to 23×25	347 to 393	4 yrs.	36
Case 9	15×16 to 15×18 to 14×18	215 to 250	1½ yrs.	24
Case 10	10×15 to 12×15		1 yr.	12
Case 7	rt. 15×23 to lt. 22×23 to rt. 22×25 to lt. 30×34	258 to 426 to 470 to 793	3 yrs.	18
Case 19	14×20 to 15×20	210 to 254	5 yrs.	18 (preop.) 6 (postop.)

* Each treatment 300r.

an increase in sellar size occurred. In one, this took place in spite of radiation and surgical removal of the tumor, and in another it occurred after adequate roentgen therapy.

A decrease in the size of the sella was noted in 8 instances. In one case (Case 17) the decrease resulted after operation and radiation, but the sella again began to enlarge three years later (*see* section on surgery). The

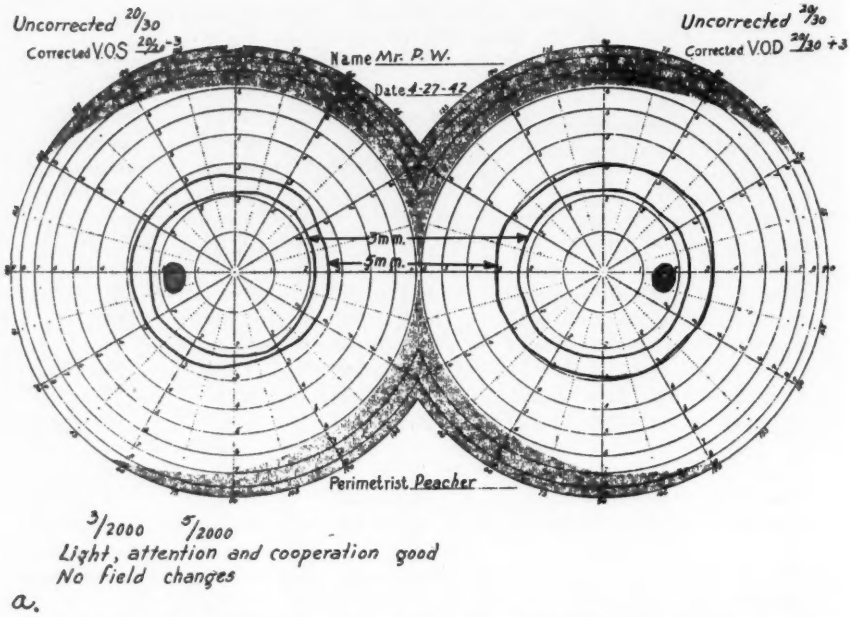

FIG. 1*a*. Visual fields. Case 7, male aged 20. April 27, 1942. First observation.

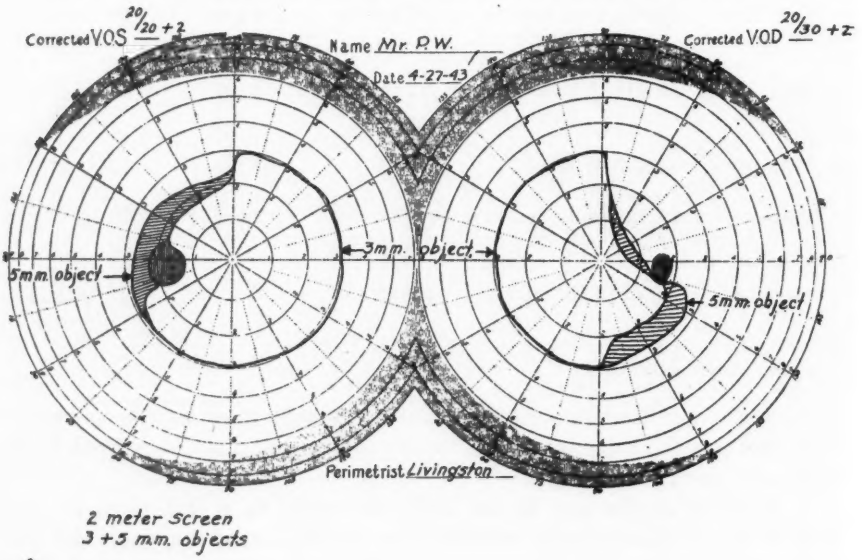

FIG. 1*b*. Visual fields. Case 7, male aged 20. April 27, 1943. Bitemporal visual field defects which should have indicated further therapy, were not noted by patient.

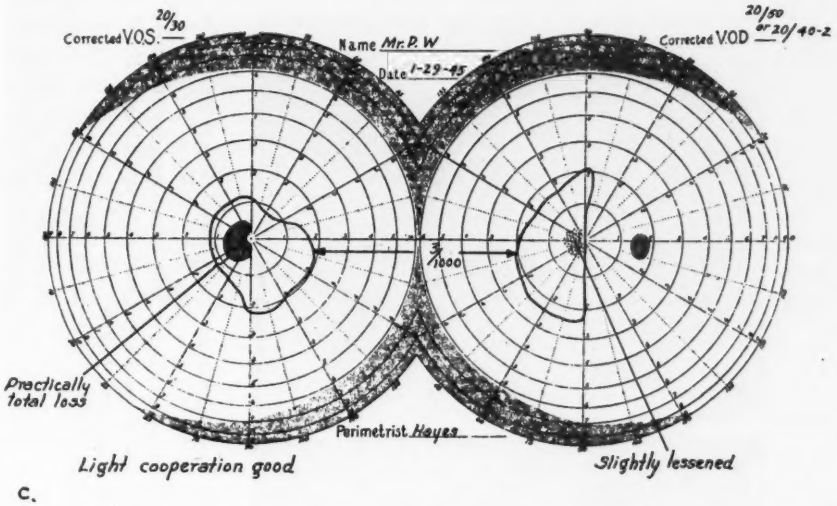

FIG. 1c. Visual fields. Case 7, male aged 20. January 29, 1945. Further decline in visual fields and acuity. Patient noted change in vision. Therapy begun.

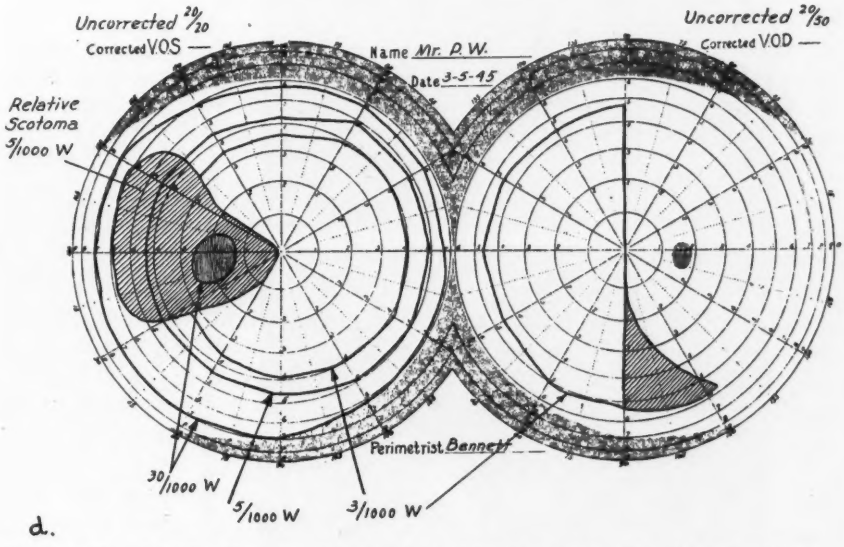

FIG. 1d. Visual fields. Case 7, male aged 20. March 5, 1945. Visual fields showing marked improvement after six roentgen treatments.

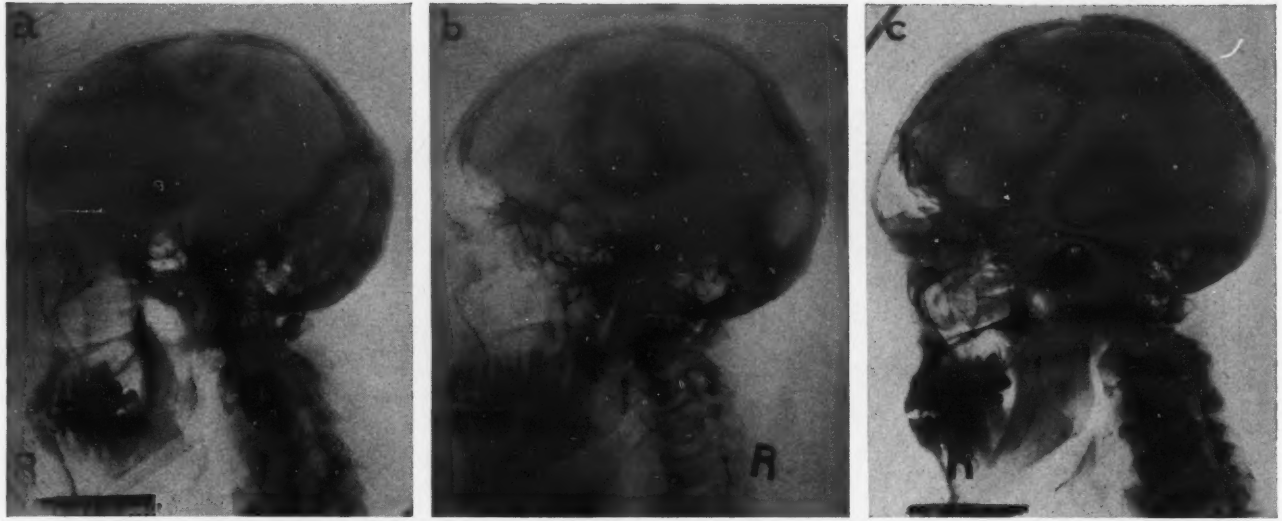

FIG. 2. Roentgenograms of skull. Case 7, male aged 20. *a.* March 19, 1942, first examination; no visual field defects (condition stationary).

b. April 27, 1943, second examination; no change in skull detail or size of sella was observed at that time by routine method; visual field defects had appeared. In retrospect, using the method of measuring the area in square millimeters of lateral contours of both sides as seen stereoscopically, there was further enlargement of the left side posteriorly (see Fig. 3).

c. January 29, 1945. Note further enlargement of sella and frontal sinuses. Marked visual field defect was present.

most marked decrease which we have seen occurred in a case of pituitary gigantism not included in this series but published elsewhere (7). Following radiation therapy the sella decreased from 23 by 19 mm. to 19 by 13 mm. Recalcification of the clinoids and floor of the sella has been noted in some cases without change in size of the sella. Such alteration probably can be interpreted as relief of pressure from the expanding tumor.

4. Headache

Headache in acromegaly follows no constant pattern. In only a few cases can it be attributed definitely to the expanding tumor, although this point

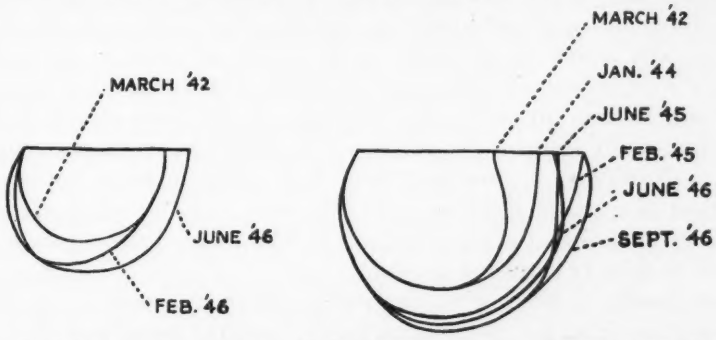

FIG. 3. Lateral contour tracings of sella turcica in acromegaly (Case 7). Note disproportional and progressive enlargement of left side. Minor changes in lateral contour area are not too significant in view of the difficulty in accurately tracing borders of sella from stereoscopic films. Contour lines represent only those in which a change was noted from previous films.

is difficult to settle. Evidence of local pressure is found in some cases at operation when not suspected beforehand. The finding of increased spinal fluid pressure is, of course, an indication for air-injection studies in order to detect any intracranial extension of the tumor. The variability of headache suggests its hormonal origin in some patients. Relief can be expected, at least temporarily, following radiation but one has to consider the possible psychic effect of this treatment in evaluation of such a subjective symptom. Other objective changes are more reliable for determining effectiveness of radiation but such changes are not always forthcoming.

In only one of our cases was headache completely alleviated for a period of two years after the last series of radiation. The greatest number of treatments given to any one patient (Case 3) was forty-two over a period of six years, with only temporary cure of headache following each series. Several patients had marked relief, but no follow-up report has been obtained as to

the duration. Others, of course, had inadequate radiation therapy, and some had sufficient amounts without results (Case 8, thirty-six treatments).

Thus, it appears that temporary relief can be obtained in some patients with a relatively small number of treatments (Case 12, twelve), whereas others require a much larger dosage. In some instances relief seems unattainable even with adequate therapy and, as occurred in one case, even surgical removal of the tumor did not completely relieve headaches. Analgesics, such as aspirin or empirin compound are rarely of great benefit.

5. Catamenia

Perhaps one of the best indications of success by radiation therapy is the subsequent re-establishment of menstruation. Tumor pressure on pituitary cells producing gonadotropic hormones or pressure upon the pituitary stalk is probably the cause of amenorrhea, rather than excess gonadotropins from an over-active adenoma. It has been shown that this symptom rarely occurs if the sella is within normal limits. Urinary gonadotropins (FSH) may be absent or reduced (8) except in those patients past the time of usual menopause; however, there is no constant pattern. A corollary exists in pituitary gigantism in which sexual development is retarded in spite of excessive growth.

Occasionally menorrhagia may develop, which if excessive, may require drastic procedures (*i.e.*, x-ray or surgery) if medical measures such as large doses of progestin or testosterone are of no avail.

6. Hyperthyroidism, diabetes and persistent lactation

Radiation therapy was given in one case of pituitary adenoma with hyperthyroidism. Although only twelve treatments were given, no improvement was noted. Another patient (Case 4) with a metabolic rate of plus 43 per cent and active diabetes, however, had a decrease in basal metabolism to plus 7 per cent, together with an apparent improvement in glucose tolerance, although the latter may well have been due to more careful diabetic management.

Persistent lactation was unaffected by roentgen therapy in one case (Case 8), but was lessened by stilbestrol in 5 mg. doses parenterally once a week. Larger doses might have been tried.

SURGERY

During the period 1932 to 1945, 5 patients with acromegaly had pituitary operations (Table 3). Two young females (23 and 28 years of age—Cases 17 and 18) had a surgical procedure because only a few acromegalic changes had occurred along with visual field defects, headache and amenor-

rhea. Both operations were followed by six x-ray treatments of 300 r each. Headaches were relieved (twenty-four months), but amenorrhea has persisted. No further acromegalic changes have resulted; in fact, there was excellent regression of tissue changes in one and moderate alteration in the other. The latter patient gained excessive weight whereas in the former, hot flashes have persisted (age 23). This patient had persistent anemia and complained of lassitude for thirty-six months after operation, but at the time of the last visit both had improved. An enlarging sella, however, indicated recurrence, for which x-ray therapy has been instituted.

In another patient, age 33 (Case 19), who received inadequate radiation therapy largely because of the inaccessibility of a place where this could be given, and because of fairly rapid enlargement of the sella with increasing headache, an operation was performed. Considerable regression of tissue changes followed but complete relief of headache was only temporary, there being some mild head discomfort when she was last seen. Menstruation returned fairly regularly in this case, as it had previously after a course of radiation therapy. Operation could be considered successful to date, so far as prevention of further acromegalic changes and restoration of normal catamenia are concerned, but only partly so with regard to headache. Only questionable visual field changes were present before operation.

A fourth patient (Case 15) had had forty x-ray treatments in two years, and then had several operations, one in 1932 and another in 1937. She died elsewhere in 1940 following an exploration attempted because she had become semicomatose. Improvement in this case followed each of the first two operations but lasted only a few years. At the first operation the tumor had extended into the floor of the third ventricle, making subtotal extirpation hazardous. Had operation been performed earlier in the course of her disease, or if more vigorous radiation had been given, this patient might have been saved.

The only male (Table 3, Case 16) subjected to operation up to 1945 was a patient aged 30 who had received no benefit from radiation therapy elsewhere; he was operated upon because of headache. Exploration revealed much edema but only a small pituitary adenoma (sella enlarged) which was not removed. Relief of headache was only temporary. He died of leukemia nine months later; his blood counts at the time of operation were normal. Acromegaly had been present only two years.

Of 4 cases in which the pituitary tumor was removed, the pathologic report was eosinophilic adenoma in 2 and mixed type in 1. The material removed in the fourth case was unsatisfactory for microscopic diagnosis, presumably because of degeneration of tumor cells.

TREATMENT OF BONY CHANGES

Osteomas may become large enough to produce symptoms and require removal. One of our patients (Case 23) had a large osteoma of the orbit and this was extirpated surgically.

Hypertrophic arthritis produced symptoms in 5 patients. Treatment in these cases is either on a symptomatic or orthopedic basis. Patients who displayed marked arthritic changes had had the disease for at least eight years or more; earlier and more persistent roentgen therapy might have retarded the development of these changes.

TREATMENT WITH ESTROGENS, TESTOSTERONE AND GONADOTROPINS

Estrogenic preparations have been given to some of our patients for various purposes. Hot flashes in women past the menopause may continue in spite of treatment for acromegaly, and estrogens are useful. In 2 cases (Cases 6 and 19) weekly intramuscular injections of 5 mg. of stilbestrol administered for several months were not successful in ameliorating headache. The same medication used for persistent lactation (Case 8) appeared to decrease the flow and to relieve headaches. A male (Case 7) received large doses of estrone sulfate and stilbestrol (up to 15 mg. daily). This produced slight breast development, some loss of body hair, and loss of the visual improvement which followed radiation therapy a few months before (Fig. 2). Further enlargement of the sella also took place so that surgical removal has since been done (1946). Cognizant of the fact that Zondek (9) produced marked enlargement of the hypophyses in rats with large doses of estradiol benzoate (given subcutaneously and percutaneously), it occurred to us that estrogen therapy might have increased the size of the tumor in this case. While estrogen therapy may inhibit the growth factor and decrease blood phosphorus as it did in one instance (Case 10, Table 1) the possibility of simultaneous enlargement of the tumor with further visual change had to be considered. The beneficial results of estrogen therapy in acromegaly have been reported by several writers (10–13).

A review of our cases in which further enlargement of the sella took place after therapy, either surgical or x-ray, shows that 6 of the 7 patients received estrogens; whereas only 1 of the 7 who had a permanent decrease in size received estrogen therapy. Whether or not estrogens are contraindicated is difficult to say, since they were administered usually to those patients in whom there might be reason to believe progression was already under way. Further observations are necessary.

We have not used testosterone in any of the male patients in this series, chiefly because none of these patients who have been under our continual

observation has developed significant hypopituitarism or secondary hypogonadism. In one female (Case 3) testosterone pellets (75 mg.) were implanted as a trial procedure for relief of headache. The patient reported sufficient improvement to desire a second implantation. From our experience in the treatment of patients with chromophobe tumors without acromegaly, beneficial results may be expected from testosterone therapy should hypofunction arise in the course of acromegaly (12, 13). Weekly doses of 50 to 100 mg. of testosterone propionate parenterally should suffice. Implantation of testosterone pellets in a dose of 150 to 300 mg. is effective and at times preferable to the parenteral method. Methyltestosterone in daily oral or sublingual doses of 20 to 50 mg. may be helpful. If evidence of adrenal insufficiency appears, desoxycorticosterone or adrenal cortical extract may be used.

Pituitary gonadotropic or chorionic preparations have not been used in any of our patients with acromegaly, although definite results were obtained in a case of pituitary gigantism (7). They might induce ovulation in cases of amenorrhea occurring from suppression of gonadotropic principles. Large doses of these preparations, either singly or combined, would have to be given. Such priming has doubtful value, although Lerman (14) believed good results were obtained with pregnant mare urine in a case of severe pituitary myxedema. In one of our cases with severe hypopituitarism, doses of from 25 to 50 units[1] per day for a period of a month failed to produce any change.

THERAPY FOR MISCELLANEOUS SIGNS AND SYMPTOMS

For lassitude, which is a frequent complaint, particularly when pituitary activity is ebbing, nothing has greater effect in our experience than benzedrine sulfate (in doses of 10 to 30 mg. per day). Desiccated thyroid, even in cases of marked hypopituitarism, may not be well tolerated and is not of great value. Anemia which occurs in the hypopituitary state seems to be unaffected by liver or iron, but may be improved slightly to moderately with testosterone. A marked improvement in anemia may indicate a recurrence of tumor growth, or reestablishment of normal pituitary function (Case 17).

Severe hypertension may occasionally be a problem and the usual palliative measures should be tried. In none of the cases in this report was there hypertension of severe degree. In a recent case showing a high diastolic pressure little benefit was derived in this regard with roentgen therapy.

[1] Courtesy of The Upjohn Company.

TREATMENT OF GOITER AND HYPERTHYROIDISM

Only 3 cases in this series showed active hyperthyroidism. Two patients were operated upon with the usual preparation and an excellent result obtained. This is not a universal experience (15). A third patient (Case 12) was a man of 40 with a very large goiter, and an initial metabolic rate of plus 70 per cent. He derived no benefit from irradiation of the pituitary or from iodine. He was given thiouracil and his condition improved. The metabolic rate dropped from plus 57 per cent to plus 11 per cent. Subtotal thyroidectomy was then performed without any postoperative reaction. The patient remained well until recently, thirty-six months after operation, when there appeared to be a recurrence of hyperthyroidism (Table 2, Case 12). The metabolic rate was plus 25 per cent. Treatment with propylthiouracil has been started. There was no obvious increase in other aspects of acromegaly or any mental or neurologic change. In a recent case not included in this series, a nodular goiter was present which caused sufficient compression of the trachea to produce stridor. The goiter was removed surgically without antithyroid drug preparation, as there was no evidence of hyperthyroidism.

MENTAL AND NEUROLOGIC CHANGES

Mental changes are probably more frequent than have been noted. It seems to us that personality changes may occur in a goodly number but may be entirely unsuspected because of their gradual development. As mentioned before, an acute psychosis followed radiation therapy in one case. Paranoia was present in another, but radiation treatment was not attempted. Our impressions as to personality deviations following radiation therapy are vague and no reliable conclusions can be drawn.

Convulsive seizures developed in 1 case but did not recur until one year after radiation therapy. No further contact has been made with this patient.

CAUSES OF DEATH

Of the 29 patients who form the subject of this report, 7 are known to be dead. The causes of death in the 7 cases were: 1) local regrowth and extension of the tumor; 2) diabetic coma; 3) pneumonia during psychotic state; 4) subacute bacterial endocarditis; 5) coronary infarction; 6) leukemia, and 7) meningitis, two months after satisfactory operation.

IMPORTANCE OF REGULAR EXAMINATIONS

Periodic examinations should be advised for all patients with acromegaly. This should be impressed upon them because of the possibility of a rapid

enlargement of the sella from the expanding tumor or sudden hemorrhage. This is not always preceded by an increase in other signs and symptoms.

Some individuals with this disorder have so few complaints and the immediate results of roentgen therapy are so slight that it is occasionally difficult to persuade them that further treatment is necessary. Goldberg and Lisser (16) particularly have stressed the importance of periodic examination of acromegalics. We wish to re-emphasize this point of view, believing that best results of treatment depend largely upon it.

CONCLUSIONS

Earlier recognition of acromegaly is paramount if prevention of the disfiguring aspects of this disease is to be expected.

The finding of an elevated blood phosphorus level may prove to be a valuable indication of active acromegaly.

Radiation therapy should be given before operation, at least for a trial period of three to six months. In young females especially, operation should be advised if the disease is not controlled after six months of adequate radiation therapy.

More intensive radiation therapy should be given than has been employed in this series of cases.

Patients with acromegaly should be seen at least once or twice a year even if asymptomatic; visual fields and roentgenologic examinations should be done.

Surgical treatment is indicated whenever irradiation therapy does not prevent progression of the disease or further enlargement of the sella.

The possibility of increasing the size of the pituitary adenoma by estrogen therapy must be considered.

Addendum

Addendum: Since this article was submitted for publication, Kinsell *et al.* have noted that the simultaneous use of testosterone and estrogen will prevent the feminizing changes which were prominent in Case 10 of this series. (Kinsell, L. W., Michaels, G. D., Li, C. H. and Larsen, W. E.: Studies in growth. I. Interrelationship between pituitary growth factor and growth-promoting androgens in acromegaly and gigantism. II. Quantitative evaluation of bone and soft tissue growth in acromegaly and gigantism, *J. Clin. Endocrinol.* **8:** 1013–1036 (Dec.) 1948.)

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THE MECHANISM OF THE SECRETION OF THYROID HORMONE*

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INTRODUCTION

THE coupling of iodine with a protein is an essential part of the activity of the thyroid gland. How this reaction leads to the formation of the hormone is nevertheless obscure, for the nature of the hormone is still unknown.

In this paper the autographic technique was used to visualize the formation of an iodinated protein in the apex of the thyroid cell and its passage into the colloid. By means of isotope dilution it was shown that this protein releases within the thyroid the amino acid thyroxine, which then enters the blood. These results point to thyroxine as being the form in which the hormone is released by the gland and circulates in the body.

Method: The various phases of this work were carried out with rats receiving Remington's low-iodine diet, which supplies about 2 micrograms of iodine daily per 100 Gm. rat. Additional animals received a supplement of 20 micrograms of iodine per day, either by injection or in the drinking water. After a minimum of six weeks on the diet, the animals were injected with carrier-free radioiodine. Two types of investigations were carried out: 1) a histologic localization of the radioiodine entering the thyroid, and 2) an attempt to identify some iodinated compounds in thyroid and blood by means of isotope dilution.

VISUALIZATION OF THE IODINE ENTRY INTO THE THYROID

The animals on the low iodine diet showed active thyroids, since histologic examination of the follicles revealed high columnar cells and narrow lumina, and the radioiodine uptake was about half the injected dose twenty-four hours after injection. The animals given a daily iodine supplement had a less active gland with lower epithelium and wider follicular lumina, and a decreased radioiodine uptake (Table 1).

The histologic location of the radioiodine was examined in the thyroid sections of these various groups of animals with the help of the auto-

Received for publication June 3, 1948.

* Read before the Annual Meeting of the American Association for the Study of Goiter, Toronto, Canada, May 6, 1948.

This article will be included in the bound volume of the "Transactions of the American Goiter Association," published by Charles C Thomas, Publisher, which will be available for sale early in 1949.

graphic technique (1). For this purpose, the histologic sections were coated with fluid emulsion and allowed to dry in the dark. The emulsion was thus bombarded by the radiations from the radioactive iodine present in the section. On development, dark silver granules overlay the sections at the sites of radioiodine deposition. This radioiodine in the sections was organically bound, since the tissues were fixed, mounted in paraffin and stained, and therefore the iodine present as iodide was extracted. The radioiodide detected by this technique was presumably bound as thyroglobulin.

The animals given a daily iodine supplement showed the presence of radioiodine in the follicular epithelium at one hour after injection. This was indicated by the circular pattern of the photographic reactions which corresponded to the arrangement of the cells (Fig. 1). Examination of

TABLE 1. FIXATION OF I^{131} IN THE THYROIDS OF RATS GIVEN VARIOUS DOSES OF IODINE

Group	No. of animals	Per cent of injected dose	
		1 hr. after injection	24 hrs. after injection
Control animals (Remington diet)	4	10.5 range (21.2–3.05)	53.5 range (58.0–43.5)
Animals receiving drinking water containing 2γ of iodide per cc.	4	1.7 range (1.0–2.4)	8.3 range (7.5–8.9)

lightly exposed sections under the high power of the microscope revealed that the radioactivity was located either at the apex of the cells or in the peripheral portions of the colloid (Fig. 2). It may be recalled here that histologists have long noted that the apex of the thyroid cell is often the site of appearance of small colloid globules staining like the colloid itself. Whereas in most of the follicles the radioactivity was located in or near the apex of the cell, it was possible to find some follicles showing a reaction throughout the colloid, especially in the central areas of the thyroid (Fig. 1).

In contrast, twenty-four hours after injection of radioiodine, similar animals revealed a uniform distribution of the radioiodine throughout the colloid of their follicles (Fig. 3). Under the high power of the microscope it could be confirmed that the black granules of the photographic reaction were most abundant in the colloid (Fig. 4).

Comparison of the results obtained at one and at twenty-four hours

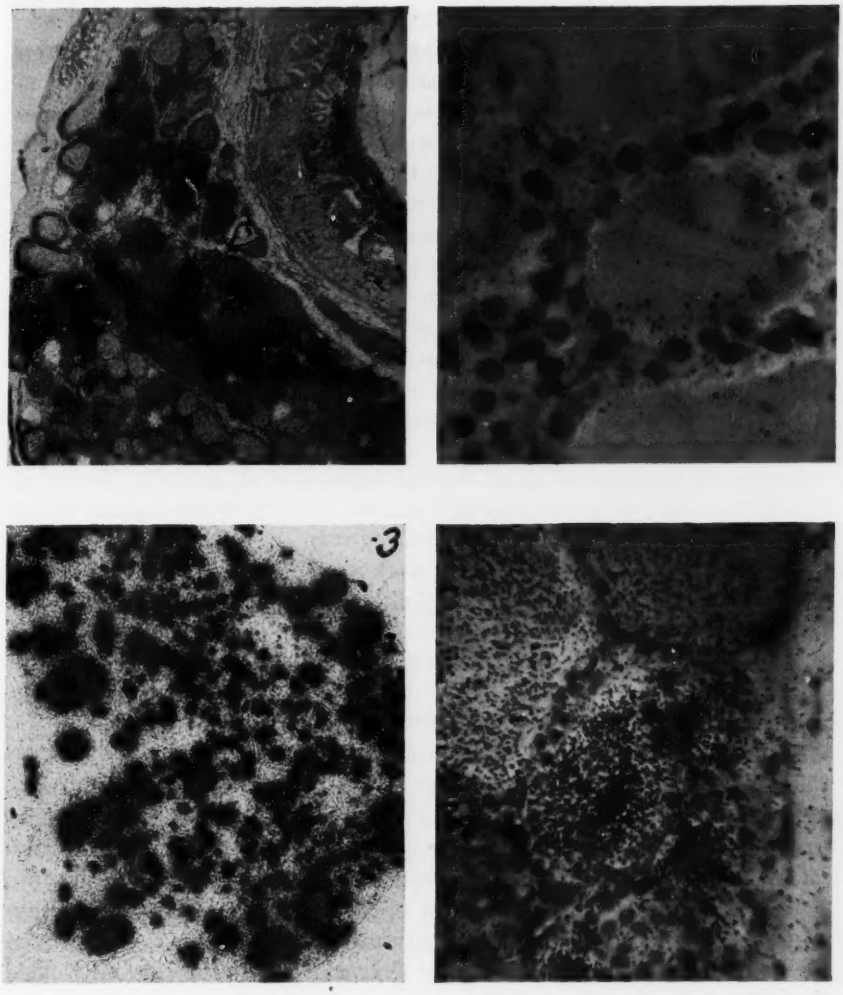

PLATE 1. These photomicrographs represent autographs of the thyroids of animals on a high-iodine diet (22 micrograms daily) given radioactive iodine. The sections have been coated with photographic emulsion which on development showed the accumulation of black granules over the site of the radioactive iodine.

FIG. 1. (about × 75) shows the thyroid under medium power at 1 hour after I^{131} administration. Note that the radioactive iodine is present in the form of rings corresponding to the outlines of the follicles. Under higher magnification (Fig. 2., × 600) the iodine can be shown in the apical portions of the cells and the periphery of the colloid. Figs. 3 (about × 75) and 4 (× 450) are corresponding autographs of the thyroid removed 24 hours after I^{131} administration. Note that now iodine is located uniformly throughout the colloid and in higher concentration (areas are blacker) than in the cells.

after injection in the animals receiving the high iodine diet made it possible to follow step by step the fate of the iodine taken up by the thyroid gland. The transformation of the iodide entering the thyroid into an organic compound—presumably thyroglobulin—was visualized in the apex of the cell. From this location the organic iodine had invaded the whole colloid twenty-four hours later (Fig. 4). It must be kept in mind that the radioiodide was carrier-free and therefore indicated the behavior of the small amounts of iodine always present in the blood. Therefore, these results revealed iodine transformations which are taking place in the thyroid gland under physiological conditions.

In the animals on a low-iodine uptake, the radioactive iodine was present in the colloid at one and twenty-four hours after injection, with no reaction being apparent in the cells. Therefore, the radioiodine must have crossed the cellular barrier and become transformed into thyroglobulin within a very short time.

A reaction was present in all thyroid follicles of all animals. Therefore, all follicles must be simultaneously active in building up organic iodine from the circulating iodide and depositing it in the colloid. Some follicles in the rat thyroid (the central ones) work at a faster rate than others (the peripheral ones). Presumably, each follicle has its own rate of formation and excretion of organic compounds, *i.e.*, its own "steady state"; but all of them are continuously contributing organic iodine to their colloid.

RELEASE OF IODIZED COMPOUNDS FROM THE THYROID

While numerous theories have attempted to explain the release of iodized compounds from the thyroid gland, De Robertis' hypothesis (2) has so far supplied the most satisfactory explanation. This author demonstrated the presence of a proteolytic enzyme system in the colloid of thyroid follicles. This enzyme was presumed to transform thyroglobulin into smaller molecules reaching the blood stream by diffusion through the thyroid cells. The recent finding of free thyroxine in the blood (3, 4) suggested the possibility that the proteolysis of thyroglobulin in the thyroid yielded thyroxine.

It is widely held that thyroxine is not present as such in the thyroid gland (5). However, it was possible that amounts of free thyroxine and free diiodotyrosine too small for chemical identification could be recovered by the method of isotope dilution. This method consists of identifying minute amounts of a radioactive substance with the help of large amounts of the same substance in an inactive form. Thus, a large amount of inactive thyroxine was added to the thyroid gland of a radioiodine treated animal and purified by successive recrystallizations. This inactive thyroxine should mix with the free radiothyroxine if present, and carry it

when precipitating or crystallizing. The absence of radioactivity in the precipitate would indicate that no free thyroxine is present in the gland. Conversely, if the precipitate were to carry a constant concentration of radioactivity, the presence of free radiothyroxine in the gland would be indicated. The constancy of the concentration is shown by the constancy of the radioactive count per microgram of substance (or specific activity) on repeated recrystallizations.

Adult rats on a low-iodine diet were sacrificed at 17 ± 2 hours after administration of a tracer dose of radioiodine. Their thyroid glands were quickly ground in the cold with 2 cc. of cold saline and shaken three times with a double volume of butyl alcohol. The butyl extract was then washed with 3 portions of 4 normal NaOH containing 5 per cent Na_2CO_3. Fifty

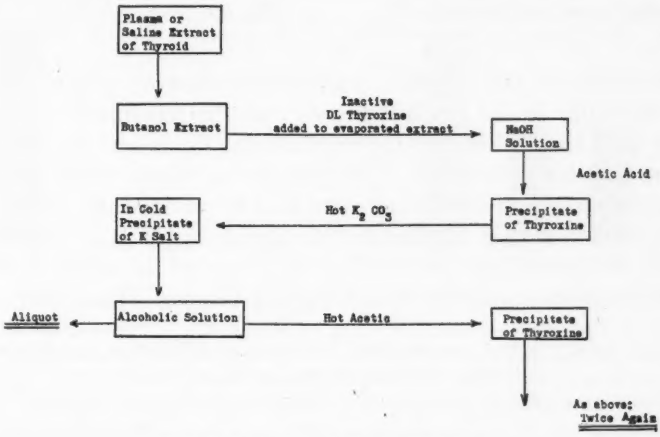

FIG. 5. Isotopic dilution of thyroxine.

milligrams of thyroxine was added to the butyl extract. Thyroxine was purified through precipitation from hot tenth-normal K_2CO_3 by cooling and from alcoholic and alkaline solutions by acetic acid (Fig. 5). This sequence was repeated three times. A fairly constant specific activity was obtained after the first precipitation series. Similar results were obtained with blood plasma, in which no initial drop in specific activity occurred (Table 2, Fig. 6). It was concluded that free radioactive thyroxine was present in thyroid tissue and plasma. The alternate possibility was that a compound very closely related to thyroxine may have behaved in a similar manner in the course of the isotope dilution.

These results are best explained by assuming that thyroglobulin is hydrolyzed with the liberation of free thyroxine in thyroid tissue. This hydrolysis presumably takes place in the colloid of the thyroid follicle, in

TABLE 2. PROTOCOL OF A TYPICAL EXPERIMENT

A female albino rat on a diet containing 0.2 microgram of iodine per gram was injected subcutaneously with a carrier-free dose of radioactive iodide. After 24 hours the animal was killed and the thyroid and plasma were treated as described in the text.

	Radioiodine content (counts per minute)	Per cent of injected dose	Per cent of I^{131} present in thyroid proteins
Residual thyroid proteins after butanol extraction	3,290,000	38.00	100.0
Thyroxine in butanol extract of thyroid suspensions (determined from isotope dilution)	35,500	0.4	1.1
Thyroxine in butanol extract of total plasma (determined from isotope dilution)	259,000	2.8	7.8

which De Robertis has identified a proteolytic enzyme system. The presence of thyroxine in the blood indicates that this substance is capable of diffusing from the follicle into the extracellular fluids and the circulation.

A more detailed comparison of the values for free thyroxine in thyroid tissue and in plasma (Table 3) indicated that the ratio of the concentration in the thyroid to that in the plasma was similar in 4 out of 5 experiments. This ratio indicated that the free thyroxine was on the average, 23 times more concentrated in thyroid tissue than in plasma. Thus, there exists a

TABLE 3. AMOUNTS OF LABELED FREE THYROXINE IN THYROID AND PLASMA AT 17 HOURS AFTER INJECTION OF RADIOIODIDE

Experiment number	Per cent of injected radioactivity present as free thyroxine		Ratio of concentration* of free thyroxine in thyroid over concentration of free thyroxine in plasma
	In thyroid	In total plasma	
1	0.08	0.54	23
2	0.20	3.44	7
3	0.38	1.42	29
4	0.13	0.47	27
5	0.08	0.34	28
Average	0.17	1.24	23

* The concentrations were calculated as the per cent of injected radioactivity present as free thyroxine per milligram of thyroid tissue or per milligram of plasma.

gradient sufficient to induce a diffusion of the material from the gland into the circulation.

Several possible causes of error had to be considered. First, there might be an exchange of iodine atoms between the radioactive iodide present in small amounts in the gland, and the large amounts of inactive thyroxine added for the isotope dilution. That this was not the case is shown in Fig. 6, in which the Roman numerals indicate the following: I is the specific

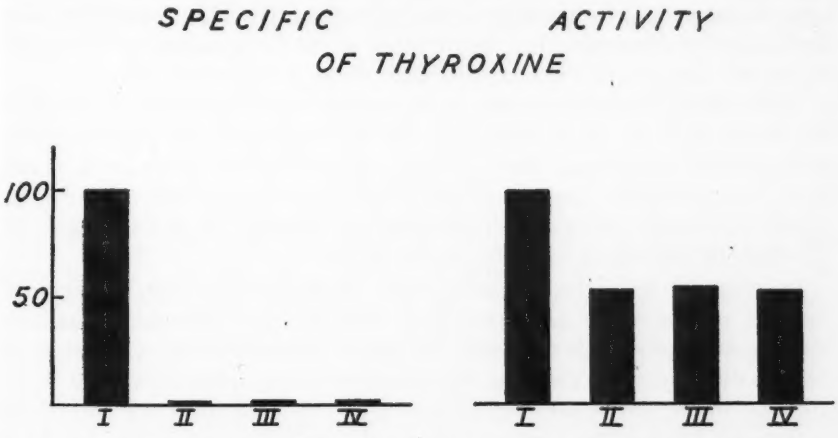

FIG. 6. This chart is a representation of the findings in the isotope dilution of the free thyroxine in the thyroid. The radioactivity per microgram of substance (*i.e.* the specific activity) is represented for the butanol or alkaline extract (I) and for subsequent recrystallizations (II, III, IV). The diagrams on the right were the values obtained in the thyroids of animals which had been injected with I^{131}. The figures on the left indicated specific activities found in control experiments, in which the thyroids of untreated rats were ground with saline containing radioactive iodine.

activity found in the original butanol extract. II, III, IV represent the specific activities on successive series of recrystallizations. The right hand graph represents the specific activities obtained in the thyroids of animals injected with radioiodine. The graphs on the left side (*i.e.* the control experiments) indicate the specific activities obtained when thyroids from untreated animals are extracted with saline containing radioactive sodium iodide. These latter dilutions showed a drop of the specific activity to less than 0.1 per cent. Therefore, there is only a very small amount of exchange, if any, in our experimental conditions; and the previous results showing the presence of free thyroxine in thyroid and plasma may not be attributed to exchange phenomena.

It may be noted here that isotope dilutions, carried out with diiodotyrosine instead of thyroxine suggested the presence of free diiodotyrosine in thyroid tissue and blood plasma. However, the possibility of exchange taking place in the case of this substance has not been eliminated. Therefore, a final decision cannot be made in regard to the presence of free diiodotyrosine in the gland.

It was possible that the relatively large amounts of radioactivity used in these experiments (on the average, 80 microcuries) might have produced some breakdown of thyroxine from thyroglobulin. This possibility was eliminated by demonstrating the presence of the free compound in thyroid tissue and blood of animals treated with doses of 0.5 microcurie.

While all these investigations were carried out in animals receiving a low-iodine diet, it was possible that free thyroxine was not present under more normal conditions, that is to say, with a higher iodine level in the diet. This possibility was investigated by repeating the isotope dilution in a purina-fed rat. Under these conditions the presence of free thyroxine in the thyroid and blood was also demonstrated.

In summary then, the following points appear. An iodinated compound may be extracted by n-butanol from unhydrolyzed thyroid tissue and plasma. On isotope dilution with thyroxine, this substance was found to behave like thyroxine through nine successive recrystallizations (*i.e.* from alkaline and alcoholic solution by means of acid, and from hot potassium carbonate solution, by cooling). While this behavior might be due to a compound closely related to thyroxine, it seems more likely that this butanol-soluble material is *l*-thyroxine itself. Since it was found that the concentration of this compound in the thyroid was considerably greater than that in the plasma, it would seem that there is a passage of thyroxine from the gland into the blood. Further, since the greater part of the plasma radioactivity was found in the butanol extract, it seems likely that this substance represents the hormone of the thyroid gland and in fact that the hormone is *l*-thyroxine

The possibility that thryoxine circulating in the plasma is bound to a protein cannot be excluded, but in view of the gentle extraction methods used, this protein-hormone combination must be very loose indeed.

CONCLUSION

The secretory mechanism of the thyroid gland includes the following steps:

1. The iodide taken up from the blood by the thyroid cell is incorporated into organically bound iodine (thyroglobulin) in the apex of the cell. It is then deposited as such in the colloid of the thyroid follicle.

2. The presence of free thyroxine has been demonstrated in thyroid tissue. This result indicates that the thyroglobulin is hydrolyzed to yield thyroxine, presumably by the proteolytic enzymes contained in the colloid.

3. The presence of free thyroxine has been demonstrated in blood plasma. The possibility that this substance originates from the free thyroxine fraction of the thyroid gland is supported by the presence of a gradient in concentration between the thyroid and blood.

4. It is proposed that *l*-thyroxine is in fact the form in which the thyroid hormone is released by the thyroid and circulates in the body.

Acknowledgment

This work was supported by a grant from the National Research Council of Canada.

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WIDTH OF ADRENAL CORTEX IN LYMPHATIC LEUKEMIA, LYMPHOSARCOMA AND HYPERTHYROIDISM

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THE recent work of Dougherty and White (1), indicating that the adrenal cortex has an important regulatory effect on lymphoid tissue, the demonstration (2, 3, 4) that cortical hormones may influence the course of experimental leukemia and lymphosarcoma, and the finding of a lowered excretion of 17-ketosteroids in lymphatic leukemia (5), raise questions concerning a possible role of the adrenals in human neoplastic disease involving lymphoid tissues.

The well-known hyperplasia of thymus and lymphoid tissue in hyperthyroidism, emphasized by Marine *et al.* (6), Warthin (7) and Friedgood (8, 9), and the suspicion on other grounds that the adrenals may be implicated in hyperthyroidism (10, 11, 12) suggest a possible interrelation of the thyroid and adrenals.

With these facts in mind, measurements of the width of the adrenal cortex were made in a series of autopsies from the files of the New England Deaconess Hospital. This was done on the assumption that the width of the adrenal cortex is correlated with its function, as indeed it seems to be in Cushing's syndrome, some cases of virilism, and in Addison's disease with so-called primary atrophy of the adrenal cortex (13).

MATERIALS AND METHODS

The material consisted of cross sections of adrenal glands taken at autopsy. They had all been fixed in Zenker's fluid with acetic acid, embedded in paraffin and stained with eosin-methylene blue, also usually with Mallory's phosphotungstic acid hematoxylin. It seemed, therefore, that the degree of shrinkage due to processing of the tissue should be uniform for the entire series. Measurements were made by means of a micrometer eyepiece, five different fields being measured on each slide and the results averaged. Cases in which the gland was distorted by postmortem changes or metastatic tumor were rejected. It was not found possible to make a clear distinction between the various zones of the cortex. No attempt was made to deduce the lipoid content from the vacuolization of the cells.

Received for publication July 10, 1948.

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The cases consisted of, first a *control group* of 50 cases, which were routine autopsies taken consecutively except for an occasional case discarded for reasons just cited. Half of these control cases were taken from the years 1933–1937, when about half of the cases of hyperthyroidism also occurred (this to control possible minor variations in histologic technique). Secondly, a group of 14 cases of *lymphatic leukemia* was studied; thirdly 13 cases of *lymphosarcoma* and *lymphoblastoma*[1]; and finally, 15 cases of *hyperthyroidism*. The latter were mostly postoperative deaths, more than half occurring within two days after either ligation or hemithyroidectomy and showing, in most instances, the clinical signs of "thyroid storm." all had severe Graves' disease, with metabolic rates averaging plus 50 per cent before operation. (In about half the cases the basal metabolic rate had been recorded within five days of operation; in other cases the high rate had been obtained two or three weeks before operation).

The results are summarized in the following table:

TABLE 1

Group	No. of cases	Mean width of cortex in mm.	Standard deviation
Control	50	1.16	0.27
Lymphatic leukemia	14	1.22	0.25
Lymphosarcoma	13	1.28	0.23
Hyperthyroidism	15	0.95	0.13

It is apparent from the table that no striking difference occurred among the first three groups, either in the means or in the degree of scatter around the mean, as indicated by the standard deviation. In the last group, however, the mean appears to be distinctly lower than the others, and the standard deviation indicates that the values are closely grouped about the mean (9 of the 15 lay between 0.8 and 1.0 mm., whereas only 9 of the 50 control cases fell in this range; also, only 1 of the hyperthyroid cases had an adrenal cortex larger than 1.16 mm., the mean for the control group).

When the control group is compared with the lymphatic leukemia group, the difference between the means is 0.06 and the standard error of the difference is 0.08, indicating no significant difference.

When the control is compared with the lymphosarcoma group, the dif-

[1] The cases in this group represent malignant neoplastic disease of lymphoid tissue, exclusive of Hodgkin's disease and lymphatic leukemia.

ference between the means is 0.12, less than twice the standard error, which is again 0.08, indicating no significant difference.

When, however, the controls are compared with the hyperthyroid group, the difference between the means is 0.21, which is 4.2 times the standard error of 0.05, indicating in all probability a highly significant difference.

DISCUSSION

If it be granted that the adrenal cortices in this relatively small group of cases of hyperthyroidism were significantly narrower than those in the control group, as they seemed to be, the reason for the difference remains to be sought.[2]

It may be objected that thyrotoxicosis and especially "thyroid storm" is a severe strain on the organism and might be expected to affect the adrenal glands. Indeed, thyrotoxicosis has been compared (14) to the "alarm reaction" of Selye (15). However, in the latter condition, no matter what the alarming stimulus, the adrenal cortex is uniformly enlarged, not narrowed (15). Furthermore, the majority of patients in the control group in this series were also exposed to considerable stress, being for the most part severely ill and frequently subjected to operative trauma shortly before death. It is true, however, that in most of the controls the termination of the illness was not as sudden or cataclysmic as in the hyperthyroid cases (12 of the 15 were operated on, and more than half died within two days after operation).

The state of nutrition of the patient might also be regarded as influencing the width of the adrenal cortex. Nine of the 15 hyperthyroid patients were described as fairly well nourished, two as "extremely emaciated" and the rest as "thin" or "poorly nourished." (As a matter of fact, one might expect an enlargement of the adrenal cortex under conditions of malnutrition since Selye has described such enlargement in the experimental animal during fasting).

It might also be objected that the control group, representing as it does a heterogeneous collection of diseases, might be overweighted with conditions thought by some to be associated with enlargement of the adrenal cortex, as for instance hypertension, cancer or infectious disease. It was found that 10 of the 50 control cases had a definite history of hypertension; the mean width of the cortex in these 10 cases was 1.18 mm. and when they were eliminated, the mean for the control group was still 1.16 mm. Eighteen of the 50 controls had cancer; the mean cortical width in these cases was 1.07 mm. and their elimination led to an increase of the mean

[2] It is recognized, of course, that the adrenals of the control group are not in any sense to be regarded as "normal."

for the remaining 32 cases to 1.21 mm. In 14 of the 50 controls a bacterial infection appeared to be the principal cause of death; in these 14 the mean cortical width was 1.23 mm., and when they were eliminated the mean for the remaining 36 was 1.14 mm. It appears probable, therefore, that the control group is not overweighted with any particular disease tending to produce enlargement of the adrenal cortex.

The literature on the size of the adrenals in hyperthyroidism, as summarized by Wegelin (16) and by Holst (17), is conflicting, but a reduction in size is described by some authors.

If such a reduction in size (or failure to enlarge) does occur, and if it indicates hypofunction, one may speculate as to whether or not it may be related to the hyperplasia of thymus and lymphoid tissue, mentioned above. Experimental evidence on this point has been difficult to secure, the results suggesting that the thyroid may play a role subordinate to the adrenals in respect to lymphoid tissue, and that there may be a reciprocal relationship between the two, such that hyperplasia of lymphoid tissue might be associated with either hypoplasia of the adrenal cortex or hyperplasia of the thyroid, or both (18, 19, 20). A reciprocal relation between thyroid and adrenals is suggested by the work of the Hoffmanns (12). Other investigators, however, have reported decrease in size of the adrenal cortex following thyroidectomy or treatment with thiouracil, and increase in size after feeding thyroid extract (21, 22).

If adrenal hypoplasia is characteristic of "thyroid storm," one may also wonder whether this hypoplasia indicates a failure of adaptation of the organism in the sense of Selye (15). Clinical evidence concerning adrenal hypofunction in thyrotoxicosis is apparently inconclusive (11, 23).

SUMMARY

The width of the adrenal cortex was measured in autopsy sections in cases grouped as follows: controls (a series of miscellaneous causes of death), lymphatic leukemia, lymphosarcoma, and hyperthyroidism. No significant differences were found among the first three groups. In the cases of hyperthyroidism, however, the adrenal cortices appeared to be significantly narrower than those of the control group. Possible reasons for this difference are discussed.

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SPERMATOGENESIS FOLLOWING THE ADMINISTRATION OF ANDROGEN AND GONADOTROPIN IN A CASE OF EUNUCHOIDISM

COINCIDENTAL NEOPLASM DURING THERAPY

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THE phenomenon of spermatogenesis achieved after testosterone and gonadotropin therapy in the eunuchoid individual whose previously untreated case of relatively severe hypogonadism is reported herewith is noteworthy. While receiving treatment, the patient suddenly developed a malignant tumor. Neoplastic growth—intriguing at all times—merits special consideration when it occurs rapidly in the wake of endocrine therapy in humans, even if the element of chance must be weighed heavily in the theoretical evaluation of possible etiology.

CASE REPORT

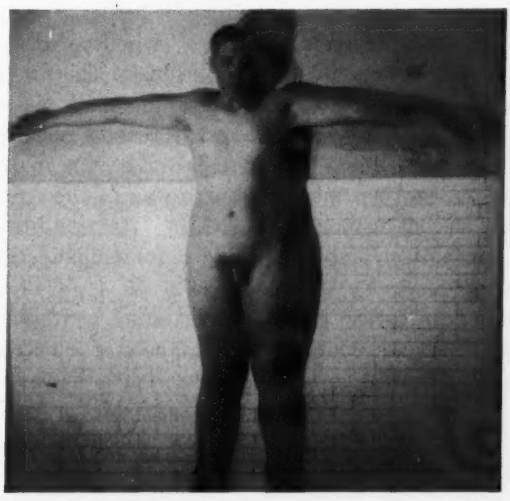

Fig. 1. 31-year-old patient with prepuberal hypogonadism—preceding therapy.

The patient (Fig. 1), a 31-year-old male American of Polish-Bohemian extraction, first examined on August 27, 1946, complained chiefly of immature and effeminate appearance, high voice, small dimensions of his external genitalia, scant growth of beard, pubic, axillary and other body

Received for publication May 19, 1948.

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hair, seemingly normal libido but potentia marred by inability to ejaculate, and psychic trauma resulting therefrom. Objective inspection rendered valid his grievances, revealing his weight of 176½ pounds, height of 69¾ inches, span of 74¾ inches, distance from floor to symphysis pubis 37¼ inches, and from symphysis to top of head, 32½ inches. The nonerectile length of the penis was 2¾ inches and the penile diameter was one inch. Testicular dimensions were: left, 1¾×1 inch; right, 2×1¼ inches. The patient possessed prominent cheek bones (Asiatic type facies), a small thin nose, and fawn-colored skin wrinkled finely around the mouth and along the jaw angles and adjacent neck areas. There were bitrochanteric and mons venerum fat pads, and moderately pendulous breasts containing fat and other subcutaneous tissue suggestive of glandular elements. Ventrally, superficial veins were prominent over the entire thorax and both axillae.

The following family and personal antecedents might have some significance: his mother died, aged 57 years from "cancer of the rectum" and his maternal grandmother "died in her 80's from cancer of the right temple." There was no other known history of malignancy.

The patient had a "severe case of mumps" when he was approximately 10 years of age. He claimed that masturbation for the first time at 14–15 years of age was climaxed by an orgasm and "normal" ejaculate. Before a year elapsed, ejaculation—for some unknown reason—became impossible; yet the patient seemed well in all other respects, having masculine habitus, strength and vigor. First sexual intercourse was at the age of 18 years—"O.K., except for lack of any ejaculate." The latter condition prevailed at the time of the present consultation. The patient engaged in coitus once each six to eight weeks.

No portion of the prostate gland was detected by rectal palpation on August 27, 1946. Extreme tenderness was evinced when the supposed area of the right upper lobe was felt. One or two drops of clear fluid were expressed from the urethral meatus onto a slide. Microscopic examination disclosed only indefinable debris. The patient masturbated unsuccessfully, trying to obtain a semen specimen.

TREATMENT AND RESULTS

Sublingual administration of methyltestosterone in propylene glycol/20 per cent alcohol (25 mg. per cc.) was prescribed.[1] From August 29, 1946 to the end of January 1947, the patient consumed 100 cc. of this product.

[1] The methyltestosterone in propylene glycol was supplied through the courtesy of Dr. W. R. Bond of the Schering Corporation.

He also applied 100 grams of ointment (2 mg. methyltestosterone per gram) percutaneously to the external genitalia, abdomen, chest and face. Therapeutic consequences were progressive almost immediately and dramatic in the positive sense. On September 28, 1946, one month after the beginning of treatment, the patient enthusiastically reported marked amelioration of his initial symptomatology. Objectively, he had gained $11\frac{1}{4}$ pounds. Penile dimensions were moderately increased. His voice seemed lower. On October 26, 1946, the patient elatedly recounted that he had ejaculated successfully shortly after his visit on September 28, 1946. Clinically, there was notable increase in masculine hair growth and musculature. The breasts seemed masculine in contour and consistency. A further weight gain of $4\frac{3}{4}$ pounds was recorded. On November 5, 1946, masturbation yielded a specimen for semen analysis performed on hanging drops and fixed smears.[2] The diagnosis was *aspermia*. Consequently, it was decided to give the patient a series of gonadotropin injections, hoping thereby to stimulate further testicular growth, function and possibly, spermatogenesis.

An initial dose of chorionic gonadotropin in the form of 1.0 cc. of A.P.L. (1,000 I.U. per cc.)[3], injected intragluteally, was followed by an injection of 0.75 cc. every second to third day thereafter until the fifteenth injection, when subsequent doses were reduced to 0.5 cc. A total of 24 injections was given, terminating on January 20, 1947. Perineal "soreness and waves of pain" through the perineum, testes and penile shaft followed several of the injections by a matter of four to six hours, persisting in a few instances until the next day. After the ninth injection, the patient remarked about his progressively increasing stamina, general sense of well being and rapidity of beard growth. By November 23, 1946, there was another weight gain of 5 pounds. The fawn-colored, finely wrinkled facial skin had assumed normal texture and complexion. Cheek bones were no longer prominent. Physical contours appeared masculine. Examination on December 20, 1946, revealed $27\frac{3}{4}$ pounds gained since therapy was started. Nonerectile penile length was $4\frac{1}{8}$ inches and the penile diameter was $1\frac{1}{2}$ inches. The testes measured: left, $2\frac{1}{8} \times 1\frac{3}{8}$ inches; right, $2\frac{1}{2} \times 1\frac{1}{2}$ inches. There was increased axillary and pubic hair, and new hair growth over the sternum, lower abdomen, dorsum of hands, arms and, especially, both thighs.

The peak of the patient's total weight gain of $31\frac{1}{2}$ pounds was charted on January 13, 1947. One week later, on January 20, 1947, he had lost

[2] All semen examinations in this case were performed by Dr. Gerson R. Biskind.

[3] The A.P.L. was supplied through the courtesy of Ayerst, McKenna & Harrison, Ltd., Rouses Point, N. Y.

4½ pounds. He received his last injection of A.P.L. on this day. On January 28, 1947, he complained of a mass in his right lower quadrant: it had appeared, he insisted, and grown rapidly during the last five to seven days. He felt that there was some relationship between this new growth and his work duties as a machinist, claiming undue pressure resulted against his right lower abdominal wall when the routinely applied heavy wrenches to various pipes. Inspection disclosed a subcutaneous tumor mass measuring approximately three inches in length and elevated one inch above the abdominal wall surface, located along the lateral margin of the right rectus muscle, about 1½ inches below the umbilicus (Fig. 2). Two possible diagnoses were considered: 1) atypical hernia, and 2) neoplasm. Surgical removal of a hematoma-like, encapsulated mass was performed on February 4, 1947 (Fig. 3).

FIG. 2. Showing right lower quadrant mass following surgical preparation.

When first seen by the pathologist, the specimen consisted of a cystic or pseudocystic structure 3.5 × 3.5 × 2.5 cm. in size, possessing a capsule composed of smooth, glistening sections alternating with areas of fibrous tags. The fibrous wall, raggedly lined, was 1 to 1.5 mm. thick. There were other numerous irregular fragments of tissue which had been dissected away from within the cavity. Some were relatively soft, friable, yellowish, glistening and homogenous; others were frankly hemorrhagic. One portion presented an organizing hematoma.

Sections were examined microscopically by the attending pathologist and two consultants (Fig. 4). The respective diagnoses were:

FIG. 3. Surgically exposed tumor mass *in situ*.

FIG. 4. Microscopic section from tumor area showing closely packed spindle-shaped cells with moderately vesicular nuclei; hematoxylin-eosin stain; Zenker fixation; ×100.

1) "*Mesothelioma (malignant)*. The most likely site of origin would seem to be a portion of isolated serous membrane along the spermatic cord. . . ."

2) "*Fibrosarcoma with peritheliomatous pattern*, probably originating in fascial tissues . . . nature . . . not entirely clear . . . no normal structure

FIG. 5. Appearance of patient three weeks following surgical excision of tumor. Note extent and rapid rate of pubic hair regrowth.

except . . . bit of distorted muscle and s.c. tissue to suggest the location or origin . . . cellularity and undifferentiated appearance of cells suggest . . . tumor is highly malignant and will undoubtedly recur. . . ."

3) "*Moderately malignant endothelioma, inguinal region (diffuse endothelial sarcoma)*." Mentioning possible sites of origin, this consultant included peritoneum, bursae, joints, but felt that the tumor cells definitely did not appear to be of testicular, spermatogenic or Leydig cell origin, and

that myoblastic or muscle origin also seemed extremely unlikely.

The patient returned periodically for subsequent endocrine follow-up. Androgen and gonadotropin therapy, ordered discontinued when the tumor mass was discovered, were not recommenced. On February 26, 1947 (Fig. 5), his weight was $21\frac{1}{2}$ pounds less than the maximum noted on January 13, 1947. On March 7, 1947, he had regained $2\frac{1}{2}$ pounds but a new subcutaneous mass, $3\frac{1}{2} \times 2\frac{1}{2}$ inches, seemed fixed beneath the recent operative scar. A course of roentgen therapy was prescribed, the patient receiving a total dosage of 3250 r to the right lower pelvis. On March 20, 1947, *two months following cessation of endocrine therapy, and after the recommended amount of X-ray treatment to the R.L.Q.*, the patient's prostate gland was definitely palpable, soft, and abnormally tender in all of its component parts. Another semen examination was requested. The following results were reported: total volume, 4.5 cc.; consistency, viscid; sperm count, 12,500,000 per cc.; motility, 10 per cent; abnormal forms, 30 per cent.

DISCUSSION

A flimsy structure, based principally on data derived from a small number of inconclusive animal experiments and inconsistent clinical experiences with humans, has been erected to support the unwarranted contention that testosterone affects adversely the seminiferous tubules of the testes and the process of spermatogenesis. Kinsell (1) recently dealt a severe blow to this structure when he reported spermatogenesis resulting in a "pan-hypopituitary" eunuchoid man from the administration of testosterone following a *supposedly proven, noneffective course of gonadotropins*. Walsh, Cuyler and McCullagh (2) and Simpson and Evans (3) were cited by Kinsell as experimental contributors to the thesis that androgens can stimulate intact germinal epithelium of the seminiferous tubules to the point of active spermatogenesis.

Attempts to explain the malignancy occurring in this case should include the ensuing considerations. The marked anabolic properties of methyltestosterone might have provided a stimulating impetus to a potentially malignant process temporarily dormant only as the result of metabolic deficiency. The A.P.L. might have been an additional stimulus, especially if the new growth derived from a terrain (perhaps embryonic cell rests) originating from the same primitive tissue layers as the gonads or other important endocrine structures. Too, the element of chronic irritation or trauma cannot be ignored. Each of the foregoing entities, alone or in combination with any or all of the others, might be of some etiologic significance. *Lastly, the possibility is manifest that the tumor occurred simultaneously with endocrine therapy purely as the result of chance.*

SUMMARY

A 31-year-old male with a clinical picture of prepuberal hypogonadism responded favorably, from the viewpoint of masculine status, to androgen and gonadotropin therapy. Especially significant was the later-proven spermatogenesis in this individual who was unable to ejaculate prior to treatment. During therapy a mass developed in the right lower quadrant and was excised surgically. Microscopic analysis proved it to be a malignant tumor. Possible etiologic factors are discussed briefly. The factual recording of this interesting sequence of events helps demonstrate anew the enigma surrounding the relationship of endocrines to neoplastic growth; moreover, it lends material bulk to the increasingly popular protest against hasty, unscientific tendencies to ascribe over-all, antispermatogenic properties to the androgens.

Acknowledgment

The author hereby expresses deep gratitude for special services rendered by Dr. Sanford E. Leeds (surgeon), Dr. Gerson R. Biskind (pathologist), Dr. Joseph Levitin and Dr. Helen B. Weyraud (roentgenologists).

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Endocrine Review

RADIOIODINE IN THE STUDY AND TREATMENT OF THYROID DISEASE: A REVIEW

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DURING the past decade many important advances have been made in our knowledge of thyroid physiology and disease. Radioiodine has been one of the important agents used in bringing about these achievements. Although only a few institutions, all of them in America, have used radioiodine extensively, a large literature has accumulated on the subject. In 1938, within four years after the preparation of the first artificial radioactive isotopes by Joliot and Curie (1) and the preparation of radioiodine by Fermi (2), Hertz, Roberts and Evans (3) in Boston and Hamilton (4) in California had made reports on the use of radioiodine in the study of human physiology. In this review we hope to bring together most of the important work which has been done in this field. Attention is called to the valuable review already published by Rawson and McArthur (5), which covers much of the application of radioiodine to thyroid physiology prior to 1947.

RADIOISOTOPES OF IODINE

About fourteen radioactive isotopes of iodine have been identified but only four have been used in biologic studies. The original investigators (3, 4, 6) used I^{128}, which has a half-life of twenty-five minutes and allows only the briefest experiments. By 1940, I^{130} with a half-life of 12.6 hours, I^{126} with a half-life of thirteen days and I^{131} with a half-life of eight days had been used (7) (Fig. 1). Because it is most available, I^{131} is now used almost universally. I^{131} disintegrates to xenon, each atom of iodine emitting a beta particle and two gamma radiations. The maximal energy of the beta particles is 0.595 MEV (million electron volts) while that of the gamma rays is 0.360 MEV (8). I^{131} is prepared at Oak Ridge National Laboratories, by bombardment of tellurium with neutrons in the chain-reacting pile. As is characteristic of the radioactive isotopes (9, 10), radioiodine acts chemically and physiologically exactly as does its stable isotope I^{127}, except for its radiation effects. With a Geiger counter (Fig. 2) or by autoradiography, quantities can be detected which are too small to pro-

Received for publication October 12, 1948.

duce appreciable radiation effects on tissue or to disturb the iodine metabolism of the test subject. One millicurie of I^{131} (which is by definition that quantity undergoing 3.7×10^7 disintegrations per second) weighs only 0.008 microgram (11). Quantities of 0.1 to 1,000 microcuries have been used for single physiologic experiments. Often a small quantity of 5 to 100 micrograms of sodium or potassium iodide is added as a carrier to the solution containing radioiodine. This is done for several reasons, one being to minimize the loss of the isotope by adsorption on glassware or other instru-

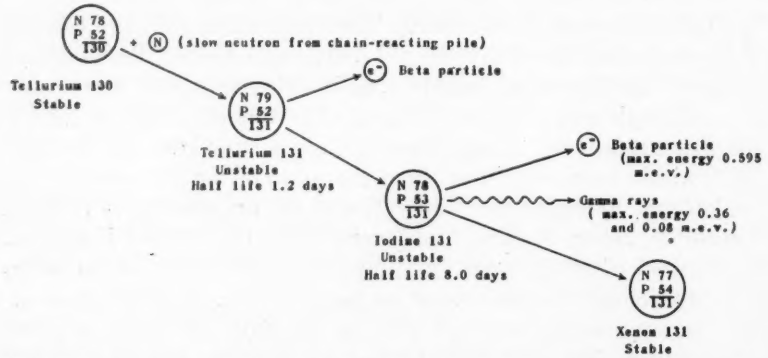


FIG. 1. The source and fate of iodine ^{131}. The nuclear structure of each atom is represented. N refers to the number of neutrons in each atom; P refers to the number of protons; the sum of the two represents the mass number for each atom. The diagram is simplified in that each atom of tellurium^{131} disintegrates by isomeric decay, which is not shown.

ments. It has not been established that this procedure is necessary, and many investigators have used carrier-free radioiodine without difficulty.

Radioiodine has a heavy homologue, astatine (formerly called Eka-iodine or element 85), which has a half-life of 7.5 hours, and emits alpha particles. Physiologically it behaves somewhat like iodine, but its uses have not been thoroughly explored (12).

FATE OF RADIOIODINE IN THE BODY

Gastro-intestinal tract.—By use of the Geiger counter Hertz, Roberts and Evans (3) and Hamilton (4) found that ingested radioiodine is rapidly absorbed in the stomach and can be detected in the human hand within three to six minutes. Absorption in the gastro-intestinal tract is 75 per cent complete in one hour and apparently complete in three hours. The presence of food in the stomach delays absorption (13). Some of the dose absorbed from the stomach is probably secreted back into the stomach,

since the stomach and salivary glands have been shown to secrete radioiodine in fairly high concentration when it is injected intravenously (14). Only a small part of a tracer of radioiodine appears in the stool, usually not more than 3 per cent and never more than 11 per cent (13, 15, 16).

Extracellular fluids.—McConahey and co-workers (17) found that concentration of radioiodine in the blood rose to a maximal level within an

FIG. 2. Measurement of radioiodine in the thyroid with Geiger counter. The counter is heavily shielded in lead. The shield has a window which is covered by a metal filter through which gamma rays, but no beta particles, may enter the counter tube. Radiations detected by the tube are counted automatically by the scaler on the right. The thick lead plug is placed over the window of the shield so that counts may be made to correct for radiation entering the tube from sources other than the target. Quantitative estimations of radioiodine in vivo are not yet very accurate.

hour after ingestion of the tracer. The curve of total radioiodine in serum plotted against time after oral administration of a dose was shown to have three components: 1) an initial rapid increase followed by a brief rapid fall, which is regarded as reflecting gastro-intestinal absorption and equilibration with body fluids; 2) an exponential fall, which is regarded as reflecting disappearance of radioiodine as iodide from the blood into the thyroid, the urine and other sites of disposal; 3) a phase which represents the appearance in the blood of organically bound radioiodine. They showed

that radioiodine disappears from the blood slowly in myxedematous patients and rapidly in hyperthyroid patients (Fig. 3). After seventy-two hours practically all of the ingested radioiodine in the blood of patients with exophthalmic goiter has become protein-bound (Fig. 4). Perlman, Chaikoff and Morton (16) suggested that radioiodine apparently diffuses passively into and out of the intercellular fluid spaces since the maximal levels in the tissues were reached at about the same time as the maximal level in the blood.

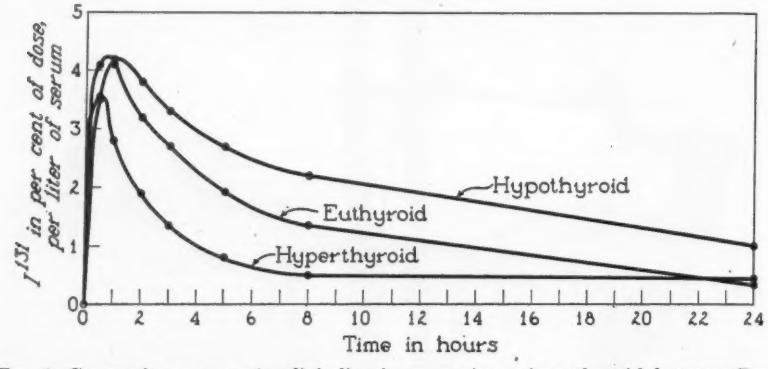


FIG. 3. Composite curves of radioiodine in serum in various thyroidal states. Radioiodine disappears from the blood more slowly in myxedematous patients than in normal subjects. It disappears from the blood more rapidly in hyperthyroid patients than in normal subjects.

Body tissues.—The original studies with radioiodine revealed that a large part of an ingested dose of radioiodine is collected by the thyroid. This will be discussed at some length in the section on metabolism of radioiodine by the thyroid. Other tissues participate to a slight extent in the collection of radioiodine. About 10 to 15 per cent of a dose of radioiodine is not accounted for by thyroidal collection and urinary excretion (18). Loss of radioiodine by technical error, by exhalation in expired air, by secretion in sweat and by excretion in feces may account for a part of this fraction of the dose but the greatest part of it probably is collected by various body tissues. Small amounts of radioiodine have been demonstrated in various organs of animals to which radioiodine had been administered, particularly in the ovaries, pituitary, lungs, kidneys and liver (19, 20). The parathyroids were not found to collect appreciable quantities of radioiodine (21). Rall and co-workers (22) measured the collection of radioiodine by various body tissues in the case of a patient who died fifty-seven hours after receiving 63 millicuries of I^{131} for treatment of advanced car-

cinoma of the thyroid. The following tissues collected radioiodine: thyroid (22 per cent of dose), thyroid malignant tissue 1.2 per cent, muscles 3.3 per cent, liver 3.9 per cent, brain 2.0 per cent, lungs 0.6 per cent and kidneys 0.1 per cent.

Urinary excretion.—Hamilton and Soley (23), as well as others (3, 7) have pointed out that a large part of an ingested dose of radioiodine is excreted in the urine within forty-eight hours, after which time only

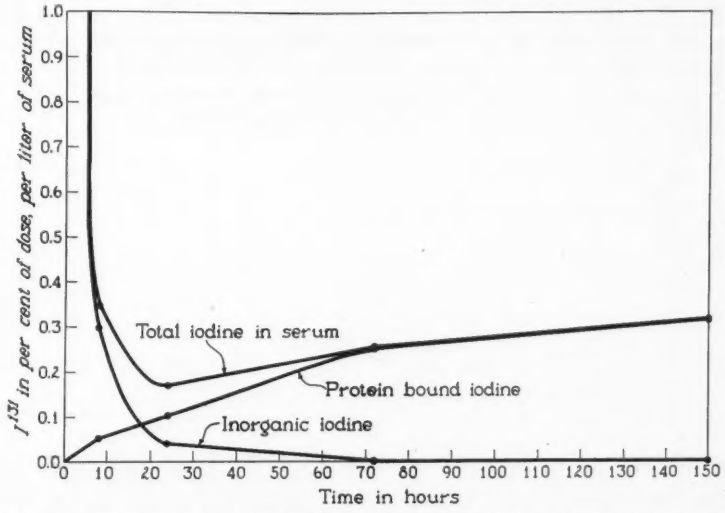


FIG. 4. The appearance of protein-bound radioiodine in the blood of a patient with exophthalmic goiter who had received a therapeutic dose of radioiodine, expressed in per cent of dose per liter of serum. The radioiodine in the serum gradually becomes protein-bound, so that at seventy-two hours virtually all the radioiodine in the serum is protein-bound and none is inorganic iodide. (From McConahey, Keating and Power (17).)

minute quantities are excreted. Keating, Power, Berkson and Haines (24) studied the urinary excretion of radioiodine using a tracer dose of 100 microcuries of I^{131} with a carrier of 100 micrograms of sodium iodide. Urine was collected at frequent intervals for seventy-two hours after administration of the dose. Knowing that all but 10 or 15 per cent of the ingested dose which was not excreted in the urine was collected by the thyroid (23), they were able to use the urinary excretion figures as an indicator of the approximate collection by the thyroid. By plotting cumulative urinary excretion against time, they obtained an exponential curve from which were estimated four factors: 1) a renal fraction (that part of the dose of radioiodine asymptotically excreted in the urine); 2) a dis-

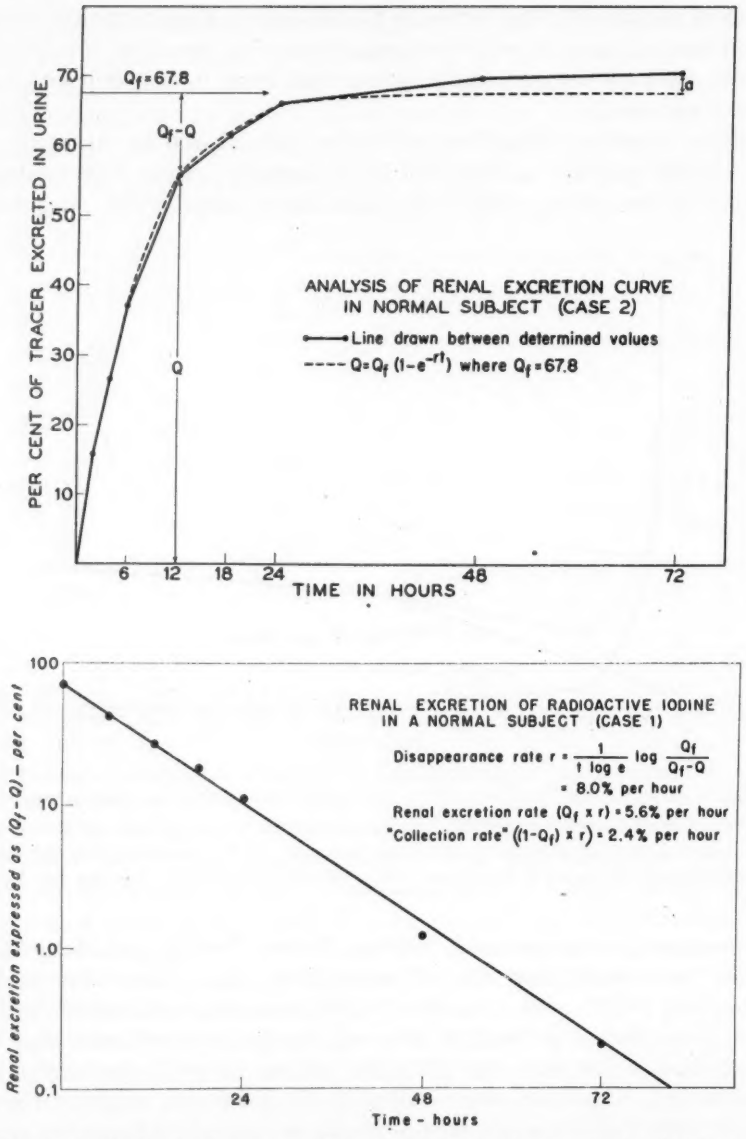


FIG. 5. Analysis of urinary excretion of radioiodine in a normal subject. A. The quantities employed in analyzing the curve: Q_f is the asymptote or plateau which the initial excretion curve approaches; the quantity $Q_f - Q$ may be plotted as a straight line on semilogarithmic paper. B. The form of the renal excretion curve when plotted as the expression $Q_f - Q$. From the line the value r, or disappearance rate, may be determined. (Modified from Keating, Power, Berkson and Haines (24).)

appearance rate (the proportional rate of disappearance of radioiodine from the blood); 3) a renal excretion rate (the proportional rate of excretion into the urine obtained by taking the product of renal fraction and disappearance rate); 4) a "collection rate" (or more properly, extrarenal disposal rate), defined as the proportional disappearance into other sites than the kidneys, of which the most important is the thyroid, obtained by taking the difference between disappearance rate and excretion rate (Fig. 5 and Table 1). In normal persons the kidneys excrete about 60 to 70 per

TABLE 1. ANALYSIS OF URINARY EXCRETION OF RADIOIODINE IN 169 PERSONS*

	No. of cases	Basal metabolic rate, per cent	Renal fraction per cent of dose	Disappearance rate, per cent per hour	Renal excretion rate, per cent per hour	Collection rate, per cent per hour
Normal volunteers	4	− 1 ±2.0	65.2±2.5	11.1±1.8	7.2±1.0	3.9 ±1.4
Euthyroid patients with carcinoma of thyroid	28	0 ±2.4	64.5±1.9	10.9±0.7	6.4±0.4	3.9 ±0.6
Adenomatous goiter:						
without hyperthyroidism	26	+ 1.8±1.8	62.1±3.8	13.1±4.8	7.3±0.5	5.7 ±1.1
with hyperthyroidism	23	+25.8±2.0	43.6±3.3	16.3±1.9	6.2±0.8	10.1± 4.1
Exophthalmic goiter	64	+39.0±1.6	23.4±3.9	30.0±3.3	5.5±0.4	24.5 ±1.9
Myxedema	24	−27.7±0.8	85.5±0.6	6.3±0.4	5.4±0.4	0.93 ±0.11

* Study of the cumulative urinary excretion of a tracer dose of radioiodine has provided valuable information on the kinetics of iodine metabolism. From these excretion curves the fraction of the tracer dose excreted by the kidneys, the disappearance rate of radioiodine from the blood, the rate of renal excretion and the rate of collection by the tissues (the thyroid principally) can be determined. This table shows what these factors are for normal subjects and for patients with thyroidal disease.

cent of the administered dose within forty-eight hours, at a rate of about 5 to 9 per cent of the circulating radioiodine per hour. The rate and amount of renal excretion are diminished when there is impaired renal function. The calculations of disappearance rate have been strikingly uniform whether based on renal excretion curves (24), thyroid uptake curves measured by a Geiger counter (18), curves of radioactivity over a peripheral part of the body (thigh) (18) or curves of disappearance from the blood measured directly from samples of blood (17) (Table 2).

METABOLISM OF IODINE BY THE THYROID

Vanderlaan and Vanderlaan (25) present the metabolism of iodine by the thyroid as a three-phase process. The first phase involves iodine accumulation; the second involves hormone synthesis and the third involves the secretion of hormone.

Iodine accumulation.—As soon as radioiodine enters the blood stream, the thyroid begins to collect it (3) and the kidneys begin to excrete it, the two organs competing for the available iodine according to their capacities to handle it (24). Hamilton (12) pointed out that the thyroid has the capacity of concentrating iodine to 10,000 times the blood level. Probably only

iodide free of protein linkage is collected selectively by the thyroid (6). Keating and co-workers (24), on the basis of calculations of the "accumulation rate," have suggested that the normal rate of iodine uptake by the thyroid is about 2 to 4 per cent per hour of the normal total iodide present in the blood and body fluids. Hamilton (12), Hamilton and Soley (13, 23) and Childs and co-workers (26) have shown by tracer studies of radioiodine with varying sized carriers of sodium iodide or potassium iodide that small doses of 100 micrograms or less of natural iodine, I^{127}, are handled efficiently by the thyroid, which collects about 20 or 30 per cent of the

TABLE 2. VALUES FOR RATE CONSTANT *r* DETERMINED FROM URINE, BLOOD, THYROID AND THIGH*

Condition	Cases	r (per cent per hour), mean†				Variability of r‡	
		Urine	Blood	Thyroid	Thigh	S.D.² variance	P
Euthyroid	6	14.5±1.1	15.0±0.8	12.9±1.1	14.0±1.0	3.76	>0.05
Hyperthyroid	7	39.0±5.3	39.3±5.5	40.6±6.6	37.0±5.1	26.84	>0.05
Hypothyroid	4	6.0±0.5	8.5±1.3	6.0±0.7	6.9±0.5	2.68	>0.05

* From: Luellen T. J., Keating, F. R., Jr., Williams M.M.D., Berkson, J., Power M. H. and McConahey, W. M. (*18*).

† The value after the ± is the standard error of the mean.

‡ The variability of r for each case was calculated as the variance (squared S.D.) of the four estimates derived (urine, blood, thigh and thyroid); the value in the table is the mean variance for the group. The P value was calculated by the method of analysis of variance to determine whether the differences among the determined *r*'s were significant statistically. A value of $P < 0.05$ is generally considered a good criterion of significance.

ingested dose within forty-eight hours. Larger doses, such as several milligrams, saturate the iodine capacity of the thyroid and are only partly as well collected (12, 26) (Fig. 6).

This accumulation of iodine by the thyroid may be divided into two components, the trapping of inorganic iodide, and the conversion and storage of organically bound iodine. Trapping is the rapid concentration by the thyroid of relatively large quantities of circulating iodide presumably in the follicle cells. If the iodide trapped by the thyroid cannot be utilized for hormone synthesis most of it passes out of the gland within twenty-four hours. Simultaneous with trapping in the normal thyroid, the trapped inorganic iodide apparently is being converted to organically bound iodide and accumulated in the form of diiodotyrosine and thyroxine in the colloid. This converted iodine accounts for more than 90 per cent of the iodine collected by the thyroid forty-eight hours after a tracer dose has been ingested and is thus responsible for the greatest part of the thyroid's ability to collect iodine. These assumptions are based on the following studies with radioiodine.

Collection of iodine by the thyroid has been studied mainly by two types of experiments: autoradiography and biochemical determinations.

Hamilton, Soley, Reilly, and Eichorn (27, 28) made autoradiographs by exposing photographic film to radiations from microscopic sections of thyroid tissue of patients who had received radioiodine. By developing the film and superimposing it on the stained sections they were able to study the localization of radioiodine in thyroid tissue. Leblond and co-workers, (29–34) as well as Evans (35) and Marinelli and others (36–40) have made several studies with autoradiography. By the use of thyroid tissue from

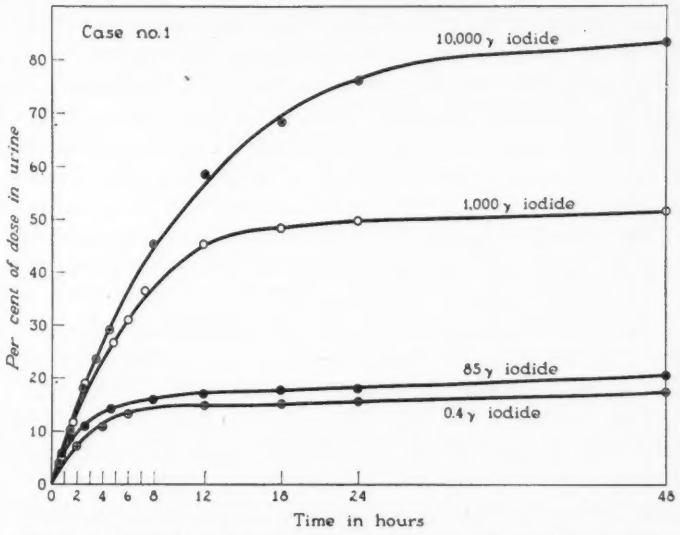


FIG. 6. Repeated tracers in the same patient showing the effect of varying the quantity of iodide in the dose as carrier. Quantities of 100 micrograms or less behave essentially alike, while larger amounts show progressively less accumulation of iodide by the thyroid. (From Childs, Keating, Williams and Power (26).)

rats (31) and from human beings (34) radioiodine was found to accumulate rapidly in, and spread diffusely through, the colloid in a stable form which was not washed out by alcohol or the usual fixation processes. This was thought to be organically bound iodide and was found in the colloid as early as thirty minutes after administration. Less than 10 per cent of the radioiodine taken up by the gland was in the inorganic form, the rest being incorporated in diiodotyrosine or thyroxine. No radioiodine was observed in the follicular epithelium. Later Gross and Leblond (30) found radioiodine in the epithelium as well as in some of the follicles of rat thyroids one-half hour after administration of the dose. Since after an interval of twenty-four hours the radioiodine was found almost exclusively in the col-

loid, it was suggested that the cells convert inorganic iodide into organically bound iodide—diiodotyrosine and thyroxine—which is stored in the colloid.

Chagas, de Robertis and Couceiro (41), using micropuncture and aspiration of colloid directly from the follicles of the thyroid of rats, found radioiodine appearing in the colloid within thirty-five minutes and reaching a peak concentration within forty hours after radioiodine had been injected into the animals. Mann and Leblond (42), by fractionation studies on thyroids of dogs given radioiodine, concluded that the iodide coming from the blood stream accumulates in the thyroid mainly as diiodotyrosine; in their opinion the diiodotyrosine fraction is the natural precursor of thyroxine. Lein (43) separated the radioiodine collected by thryoid glands of rabbits into acetone-soluble and acetone-insoluble fractions. Acetone-insoluble radioiodine was found in small quantities as early as five minutes after the injection and increased rapidly. Lein expressed the opinion that as fixed (trapped) iodine is converted to protein-linked forms, the previously saturated "fixing mechanism" (trapping mechanism) may renew its capacity to collect circulating iodine.

It remained for Vanderlaan and Vanderlaan (44) and Taurog, Chaikoff and Feller (45), working independently, to prove that the trapping by the thyroid of inorganic iodide is a process distinct from conversion to, and accumulation of, iodide in organic form. Vanderlaan and Vanderlaan found that the thyroid glands of rats in which hormonal synthesis is blocked by propylthiouracil (see section on Antithyroid Drugs) are still capable of concentrating (or trapping) large quantities of iodine when potassium iodide is injected. This iodine is held in the reduced form as inorganic iodide. Thiocyanate, which inhibits the collection of iodide by the thyroid, was shown to cause rapid discharge of the trapped inorganic iodide, but did not release organically bound iodide.

Taurog, Chaikoff and Feller (45) presented almost identical results; thyroids of rats made goitrous by feeding propylthiouracil concentrated injected iodine despite a complete block in synthesis of organic iodine compounds. Radioiodine entered and left the thyroid to form a curve which paralleled that of radioiodide in plasma, suggesting an equilibrium between the two. Both curves depicted a maximal concentration within one half hour and fell rapidly thereafter so that nearly all the tracers had left the thyroid after twenty-four hours. The trapped iodine, which was taken up by the thyroid and discharged from it within twenty-four hours, is thought to be in inorganic form or possibly bound to protein by a labile linkage.

Hormone synthesis.—The thyroid is said to contain iodine in only three

different chemical forms (42, 46): 1) a small proportion of trapped inorganic iodide, less than 10 per cent; 2) thyroxine, representing about 25 per cent, and 3) the remainder as diiodotyrosine. It is assumed that thyroxine and diiodotyrosine share in the formation of the protein molecule of thyroglobulin, and that diiodotyrosine is a precursor of thyroxine. The results of radioiodine studies are compatible with these views. As studies on accumulation of radioiodine by the thyroid have shown, inorganic radioiodine undergoes conversion to diiodotyrosine and thyroxine rapidly; this begins almost as soon as the thyroid collects iodine from the circulating blood (34, 42, 43). Perlman, Morton and Chaikoff (47) studied the rate at which the thyroid glands of rats and sheep given radioiodine produce diiodotyrosine and thyroxine. Of the injected radioiodine, 1.5 to 3.0 per cent was present as radiothyroxine in the rat thyroid within two hours after administration. Formation of thyroxine in the sheep occurred at a slower rate. The amount of newly formed thyroxine increased with time up to 19 per cent of the total dose of radioiodine in forty-eight hours. Even a larger amount of radiodiiodotyrosine was formed. Despite considerable fluctuation in the actual amount of radioiodine deposited as thyroxine and diiodotyrosine in the gland, the proportion of the total labeled iodine represented by each of these fractions remained fairly constant at each interval. Mann and Leblond (42) gave carrier-free doses of radioiodine to dogs and found the diiodotyrosine fraction of radioiodine in the thyroid to be relatively high (8 to 11 per cent) at one-half hour, 10 to 15 per cent at eight hours and 43 per cent at forty-eight hours. The thyroxine fraction was 0.3 to 0.4 per cent at one-half hour, 1.0 per cent at eight hours and 2.4 per cent at forty-eight hours. Considering relative specific activity there was a gradual increase to a relatively higher level of thyroxine. When dogs were given excessive doses of iodine comparable to those used as therapy in medical practice, the iodine was thought to be incorporated in the glands, probably as stored iodide. The proportion of iodine transformed to diiodotyrosine was much smaller for the larger dose than in the case of the smaller dose. Taurog and Chaikoff (48) constructed specific activity-time curves for the iodine of the thyroxine and diiodotyrosine fractions of the thyroid glands of rats that had received a dose of radioiodine. The curves satisfied Zilversmit's criteria for a precursor-product relationship (49), thus providing further evidence that diiodotyrosine is the precursor of thyroxine. Studies on thyroid slices have shown that the conversion of iodide to diiodotyrosine and thyroxine is a function of cellular organization as it does not take place in homogenates (50).

The possibility of ionic exchange of inorganic and organic iodine to confuse these results is not likely but has not been disproved. Miller and co-

workers (51), using radioiodine with in vitro studies, found an exchange of iodide ions between iodine and diiodotyrosine at a pH of 4 to 5.5. Another bit of interesting information is the evidence of formation of thyroxine and diiodotyrosine in completely thyroidectomized animals. In rats several months after thyroidectomy I^{131} tracer studies revealed newly formed radiodiiodotyrosine and radiothyroxine. As early as ninety-six hours after injection 30 per cent of the I^{131} contained in the liver and

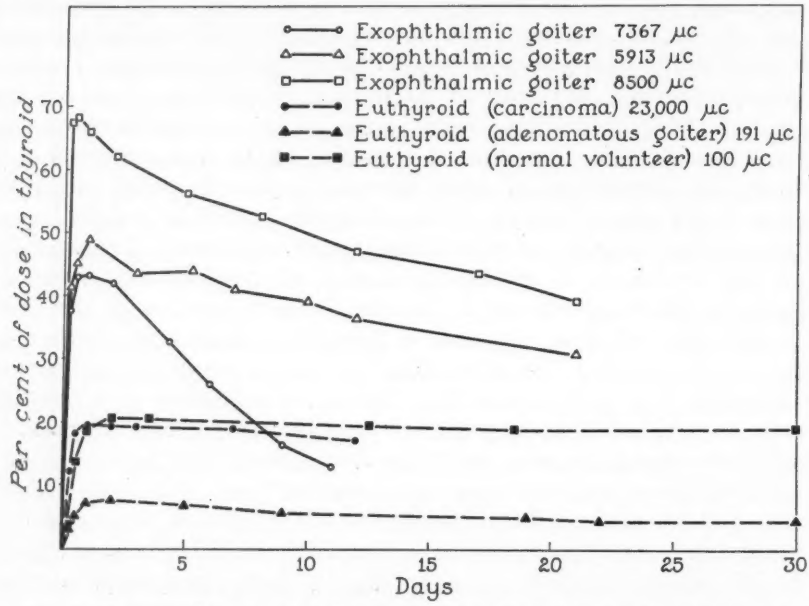


FIG. 7. The secretion of radioiodine previously collected in the thyroid appears to take place more rapidly in patients with hyperthyroidism than in euthyroid persons. These curves cannot be regarded as completely demonstrating this fact, since the radiation effects of radioiodine in the therapeutic dose given may have increased the rate of iodine secretion by the thyroid.

small intestine was organically bound, about 20 per cent as diiodotyrosine and 8 per cent as thyroxine (52). McConahey and co-workers (17) followed the plasma levels of inorganic and organic iodide of a myxedematous patient who presumably had no functioning thyroid and found a gradual conversion of inorganic to organic iodide during a period of several days.

Secretion of hormone.—Although the collection by the thyroid of a tracer dose of radioiodine without carrier is completed within a day or two, the radioiodine is liberated into the blood stream apparently as hormone

at a much slower rate (Fig. 7). Perlman, Chaikoff and Morton (16) found that at two hours after intraperitoneal injection of radioiodine into guinea pigs there was newly formed radioactive diiodotyrosine and thyroxine in the plasma. After twenty-six hours 50 per cent of the circulating radioiodine was present as radiothyroxine. The distribution of radioiodine in the organic and inorganic fractions in the tissue resembled that in the plasma (20). Mann, Leblond and Warren (46) calculated that 1.55 per cent of the thyroxine contained in a normal thyroid of a dog is formed each hour. Taurog, Chaikoff and Entenman (53), by injection into dogs of plasma of rats containing naturally biosynthesized protein-bound radioiodine, estimated a turnover of circulating protein-bound iodine each four to seven and a half hours. In their experiments with specific activity-time curves, Taurog and Chaikoff (48) estimated the rate of secretion of thyroxine by the thyroid of rats to be about 2 micrograms per 100 Gm. of body weight per twenty-four hours. Further work is needed before these results will be correlated. Johnston (54) has emphasized that measurements of stable and radioactive iodine in blood and tissue provide a ratio of specific radioactivity which is valuable in determining turnover rates of radioiodine by the thyroid.

Taurog and Chaikoff (55), by using extraction methods on plasma of rats given I^{131}, concluded that 90 per cent of plasma iodine behaves like thyroxine in solubility properties. This is offered as proof that thyroxine is the actual circulating hormone. Leblond and Gross (56) came to the same conclusion by similar experiments.

FACTORS INFLUENCING METABOLISM OF RADIOIODINE BY THE THYROID

Thyrotropic hormone.—Hertz and Roberts (57) injected thyrotropic hormone into rabbits and found an increase in the uptake of radioiodine by the thyroid, as well as an increase in follicle cell height, size of the thyroid and metabolic rate. These factors all paralleled the amount of thyrotropic hormone given except for the collection of radioiodine, which reaches a peak beyond which it cannot increase. Pretreatment with iodine lessened the effect of thyrotropic hormone in producing these changes; if administration of thyrotropic hormone was continued without iodine, exhaustion of the thyroid eventually took place and it lost its capacity to collect iodine.

Keating and co-workers (58, 59) have found, in chicks, that with increasing degrees of stimulation by thyrotropic hormone there is a progressive increase in collection of radioiodine by the thyroid until a plateau is reached. Daily injections of thyrotropic hormone cause thyroid hypertrophy (increased follicle cell height) within twenty-four hours, but iodine uptake is not increased until forty-eight hours after administration of

thyrotropic hormone begins. Apparently, rapidly proliferating thyroid tissue has a diminished capacity to collect iodine from the blood. I^{131} uptake increases as long as cell height increases (hypertrophy), but there is no increase of I^{131} uptake with further enlargement of the gland (hyperplasia). Increase of collection occurs only after hypertrophy has taken place. Thyrotropic hormone produces prompt and early acceleration of loss of previously stored I^{131} from the thyroid. This may be a measure of accelerated secretion of thyroid hormone from the gland induced by thyrotropic hormone stimulation (59).

Cortell and Rawson (60) stated that exogenous thyroxine depresses both the amount of thyrotropic hormone available to the thyroid and the action of the thyrotropic hormone available on the thyroid. Morton, Perlman and Chaikoff (61) demonstrated that injections of thyrotropic hormone increase the amount of radioiodine which becomes organically bound in the thyroid and in the plasma. Leblond and Süe (6) and others (62) found that hypophysectomy diminishes the uptake of radioiodine by the thyroid, and Vanderlaan and Vanderlaan (25) stated that thyrotropic hormone is necessary for the synthesis of thyroid hormone.

Antithyroid drugs.—Radioiodine has been a great aid in studying the action of these agents on iodine metabolism. Likewise the antithyroid drugs have aided in the study of iodine metabolism, particularly in clarifying the trapping of iodine by the thyroid (see section on Metabolism of Iodine by the Thyroid). Rabbits were found to have an increased thyroidal uptake of radioiodine when fed cabbage or methyl cyanide (7). Anaerobiosis and substances that inhibit cytochrome oxidase, including cyanide, azide, sulfide and carbon monoxide, have been found to depress the formation of radioactive diiodotyrosine and thyroxine by thyroid slices bathed with radioiodine. Apparently this function is linked with aerobic oxidations in which the cytochrome-cytochrome oxidase system is involved (63). The xanthine oxidase system may enter into the process of iodinating protein (64). Cyanide and sulfide also markedly inhibit the accumulation of radioiodine by thyroid slices while azide and sulfonamides, although preventing conversion to diiodotyrosine and thyroxine, do not prevent the uptake of radioiodine (65–67). These findings are further evidence that the thyroid has a mechanism for concentrating iodine that does not depend on the conversion of inorganic iodide to organically bound iodide.

Several studies of the effect of thiocyanate on iodine metabolism, all under different circumstances, have given apparently conflicting results. It appears that administration of a single dose of thiocyanate markedly depresses the uptake of iodine and its conversion to diiodotyrosine and thyroxine by the thyroid, while prolonged administration to the point of producing compensatory thyroid hypertrophy (thiocyanate goiter) some-

times, but not always, results in an increase of the uptake of radioiodine by the thyroid (68).

Among the acute experiments is the study of Franklin, Chaikoff and Lerner (69). Thiocyanate depressed the uptake of radioiodine and its conversion to diiodotyrosine and thyroxine in surviving tissue slices of thyroid. Rawson and co-worker (5) reported that radioiodine uptake by thyroids of chicks and rats was depressed from one to six hours after a single dose of thiocyanate, but the block in iodine collection is not demonstrable after twelve hours. McGinty and co-workers (70) found inhibition to the collection of radioiodine by chick's thyroid after a 10 mg. dose of potassium thiocyanate to be practically gone after twenty-four hours. Vanderlaan and Bissell (71) depleted the rat thyroid of hormonal iodide by administration of propylthiouracil and then demonstrated a marked inhibition by thiocyanate on uptake of radioiodine.

Goiter caused by prolonged administration of thiocyanate was first studied with radioiodine by Rawson, Hertz and Means (72). They observed increased uptake of radioiodine by a large thiocyanate goiter in a patient having hypertension who was still under treatment with potassium thiocyanate. Development of goiter was attributed to block of thyroid hormone formation by thiocyanate and consequent lowering of circulating hormone. This led to stimulation of the pituitary to produce an excess of thyrotropic hormone, thus causing hyperplasia of the follicular epithelium. These writers expressed the belief that an excess of iodine may force the block on hormone formation and cause liberation of thyroid hormone. They suggested that thiocyanate goiter might be prevented by prophylactic doses of iodine or by substitution therapy with thyroid. Rawson, Tannheimer and Peacock (73) found increased thyroidal uptake of radioiodine in rats made goitrous by thiocyanate in drinking water. Later work by Rawson and co-workers (74) indicated that the total uptake of radioiodine by rats fed thiocyanate over a long period was about the same as that of untreated controls, but somewhat less per milligram of thyroid tissue. In the chick, potassium thiocyanate fed over a prolonged period was found to be a potent goitrogen, causing considerable increase in total uptake of radioiodine and in uptake per gram of tissue.

On the other hand Wolff and co-workers (75) reported that the iodine-concentrating capacity of the thyroid is depressed in rats treated with thiocyanate, provided high concentrations of the drug are still present in the circulation. Within sixteen to twenty-four hours after the last dose when thiocyanate is no longer demonstrable in the blood, the enlarged gland has a greater than normal capacity for concentrating radioiodine. Vanderlaan and Bissell (71) tested the effect of varying doses of iodine on thiocyanate block in rats made goitrous with propylthiouracil. The larger

doses of iodide overcame the block and resulted in uptake of iodine by the gland. We have found great variability in uptake of radioiodine by human thiocyanate goiters. In some instances a low uptake when the blood thiocyanate level was high was followed by a normal, or by an abnormally high, uptake soon after the thiocyanate had disappeared from the blood.

The confusion concerning iodine uptake by thyroids treated with thiouracil seems to be resolving itself. Thyroids of patients given thiouracil in preparation for removal of exophthalmic goiters were found to collect little radioiodine (76). This was confirmed by experiments on animals (73, 77–79) and it appeared that thiouracil prevented the uptake of iodine by blocking the formation of iodinated thyroid hormone (5). In vitro studies with thyroid slices in a bath containing thiouracil had shown normal uptake of inorganic iodide by the thyroid but a failure of conversion from iodide to diiodotyrosine and thyroxine (69, 80). These relationships were clarified when it was shown that the trapping of iodine by the thyroid remains intact and is even enhanced under the influence of thiouracil while the synthesis of organic iodide is blocked by the drug (44, 45, 71).

Stanley and Astwood (81) and Williams and co-workers (82, 83) have been able to utilize uptake of radioiodine by human thyroids as a means of determining the potency of antithyroid compounds in man. Another important contribution to the knowledge of treating exophthalmic goiter has been the finding by Rawson and co-workers (84) that iodine, when given simultaneously with thiouracil, has an involuting effect on the hyperplastic gland. These authors concluded from this observation that the involuting property of iodine depended on the reduced, rather than the oxidized form.

Other factors.—Pretreatment with, or overwhelming the thyroid with, iodine causes a diminished uptake of a dose of radioiodine (7, 85, 86). An iodine-deficient diet, however, increases thyroidal iodine collection (87). Thyroid slices exposed to varying concentrations of natural iodine (I^{127}) are inhibited in their ability to convert iodine to diiodotyrosine and thyroxine when the amount of inorganic I^{127} in the medium surrounding the slices exceeds 20 micrograms (88). Recently Wolff and Chaikoff (89–91) have extended this study to rats and have demonstrated that the thyroid traps iodide but does not convert it to organic iodide as long as the serum concentration of iodine exceeds 35 micrograms per 100 cc. This phenomenon in normal animals is offered as a possible explanation for the beneficial effect of iodine in human hyperthyroidism. Administration of large quantities of iodine after a dose of radioiodine has been collected by the thyroid may hasten the urinary excretion of radioiodine from the subject (92). This is especially true if the iodine is given within twenty-four hours after the dose of radioiodine, while there is a much smaller urinary excretion of

radioiodine if the supplementary iodine is not given until seventy-two hours after the dose of radioiodine (93). Vitamin A deficiency in rats has been reported to cause an abnormally high level of inorganic iodide and a low level of thyroxine in the thyroid gland (94). Physiologic processes which increase the metabolic rate, including pregnancy (7) and exposure to cold (95), cause an increase in thyroidal uptake of radioiodine. Depressing the metabolic rate by exposure to warmth decreases iodine uptake (95). Administration of thyroid extract decreases uptake of radioiodine by the thyroid (96, 97).

At the present time it cannot be said with certainty that the radiation effects of radioiodine may not modify the results obtained by tracer studies. Tracer doses of 100 microcuries of I^{131} subject the thyroid to appreciable amounts of radiation. Skanse, Merrill and Evans (98) studied the effect of 0.1, 1 and 5 microcuries of I^{131} on the thyroid's growth, iodine content and response to thyrotropic hormone in cockerels. Thyroids collecting 0.1 microcurie were not altered in growth or iodine concentration. Those collecting 1 and 5 microcuries exhibited no increase of thyroid weight after stimulation with thyrotropic hormone and the 5 microcurie dose also prevented the loss of thyroidal iodine which thyrotropic hormone causes in normal animals. These doses represent radiation varying in quantity from 1,700 r.e.p. (roentgen equivalent, physical) to 8,500 r.e.p.

RADIOIODINE AS A LABEL FOR ORGANIC COMPOUNDS

Frieden, Lipsett and Winzler (99) have reported a method of preparing radiothyroxine by exchange reaction. Gross and Leblond (100) administered radiothyroxine by oral and intravenous routes to rats and noted the subsequent distribution of radioiodine in various tissues. Radiothyroxine disappeared from the blood rapidly. Within two hours more than 50 per cent of the radioiodine accumulated in the gastro-intestinal tract, liver and pancreas, mainly as thyroxine, except in the stomach where most of the radioiodine fraction appeared as inorganic iodide. Thyroidal collection was slight and lagged, indicating that there was probably conversion to inorganic form before the radioiodine was collected. At twenty-four hours, 80 per cent of the injected material was found in the feces and 11 per cent in the urine.

Hamilton, Albert, Power, Haines and Keating (15) treated a myxedematous patient with iodocasein and completely controlled the myxedema. The fate and distribution of a tracer dose of radioiodocasein were followed in this patient before and after control of myxedema and compared with the results of tracer doses of inorganic radioiodine. Distribution of inorganic radioiodine typical of myxedema was observed both prior and subse-

quent to control of myxedema. The bulk of radioiodide eventually appeared in the urine with little in the feces. More than half of the radioactivity from the radioiodocasein appeared in the feces and smaller amounts in the urine both prior and subsequent to control of myxedema. An appreciable quantity of the radioactivity was concentrated over the liver, suggesting an intermediate stage in the metabolism of iodocasein.

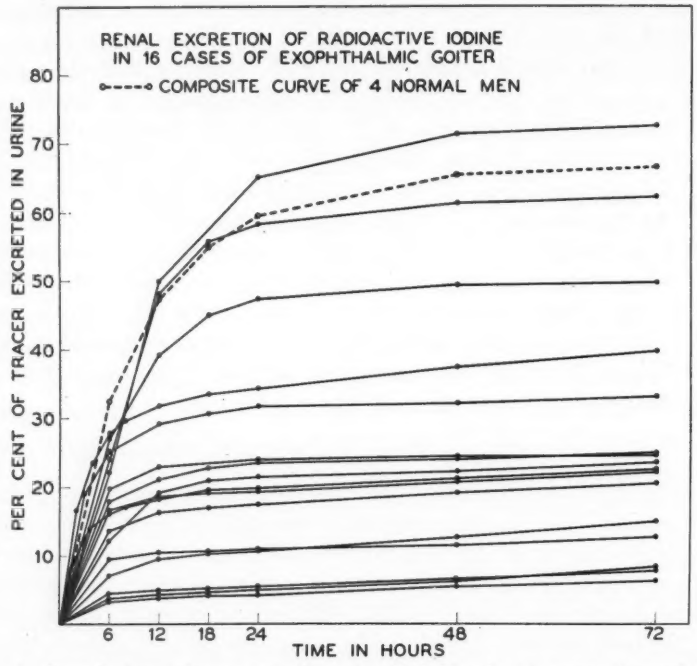


FIG. 8. Cumulative urinary excretion of radioiodine in 16 cases of exophthalmic goiter. All but 3 subjects excreted less than 40 per cent of the tracer dose. The composite normal excretion was about 65 per cent of the tracer dose. In cases of hyperthyroidism urinary excretion of radioiodine is essentially complete in a much shorter period than among normal persons. (From Keating, Power, Berkson and Haines (24).)

RADIOIODINE STUDIES IN VARIOUS THYROIDAL STATES

Hamilton and Soley (13), in their early studies with radioiodine, applied three technics which have made the clinical use of radioiodine practical: 1) determination of urinary excretion of radioiodine, 2) determination of radioiodine uptake by the thyroid in patients by use of the Geiger counter and 3) analysis of excised thyroidal or carcinomatous tissue by autoradiography or by quantitative measurement of radioactivity.

Hyperthyroidism.—Increased iodine-collecting function of the thyroid is

exhibited in hyperthyroidism by low urinary excretion of a tracer dose of radioiodine (24, 85) and by a high count of radiations over the thyroid (18, 101) (Figs. 8 and 9). Hamilton and Soley (12, 23) found a rapid and high uptake of orally administered radioiodine by the thyroids of thyrotoxic patients. When the carrier dose was large (14 mg. of sodium iodide) the high concentration of radioiodine by the thyroid diminished rapidly within a few hours, while with a small carrier (0.1 microgram) the radioiodine concentration remained high for at least several days. Hertz and co-worker (85, 102), using a small carrier dose, observed collections of radioiodine by some exophthalmic goiters to be 80 per cent or more of the dose.

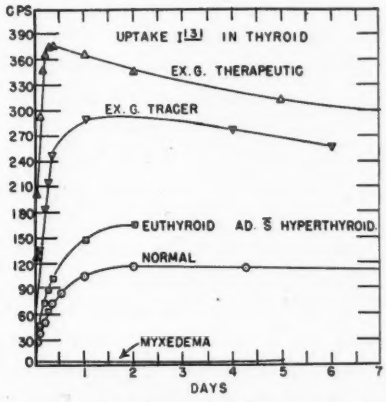


FIG. 9. Uptake of radioiodine by the thyroid measured with a Geiger counter and recorded in counts per second per millicurie dose (CPS). The uptake in exophthalmic goiter greatly exceeded the uptake in a normal subject. Uptake by an adenomatous goiter of a euthyroid subject was near normal, whereas practically no radioactivity was concentrated in the neck of a myxedematous subject.

Keating and co-workers (103) have compared various ways of measuring the iodine-accumulating function of the human thyroid. Pointing out that the thyroid collects iodide at a constant rate which is proportional to the concentration in plasma, they suggested that the most precise measure of this function is probably thyroidal iodide clearance defined as the volume of plasma cleared of iodide by the thyroid per unit time. This value is derived from serial observations of blood in addition to in vivo observations of the thyroid. They found that the most appropriate measure of accumulating function which could be obtained from thyroidal observations alone was the iodide-accumulation rate defined as the proportional rate at which the thyroid accumulated iodide. Other measures of accumulating function,

such as the *quantity* collected by the thyroid, they found to be relative rather than quantitative and modified by iodide disposal via urine and other tissues.

Normal values for thyroidal iodide clearance were not given; 3 euthyroid patients with nodular goiter had clearances varying from 2 to 13 cc. per minute, while 5 patients having exophthalmic goiter had clearances varying from 20 to 228 cc. per minute.

Using urinary excretion of radioiodine at the end of seventy-two hours as an indicator of thyroid uptake, Hertz and Roberts (104) found that in 23 of 29 cases more than 50 per cent of the dose was retained. Chapman and Evans (105) reported more than 50 per cent retention under similar circumstances in 11 of 12 cases. Means (106) described a diagnostic test devised by Skanse in which the urinary excretion for 48 hours after administration of a tracer dose of radioiodine varied between 6 and 32 per cent of the dose in 25 thyrotoxic patients. Keating, Berkson, Power and Haines (24) found the urinary excretion for seventy-two hours after oral administration of a tracer dose of radioiodine to be less than normal in 14 of 16 cases of hyperthyroidism (Fig. 8). Most hyperthyroid patients retained from 75 to 95 per cent of the tracer dose. Only occasionally did hyperthyroid patients retain normal quantities of radioiodine (about 65 per cent) and this finding may have been the result of previous treatment with iodine. The rate of uptake of radioiodine from the blood by the hyperfunctioning thyroid may be increased from the normal figure of 4 per cent per hour to 30 per cent per hour. Stanley and Astwood (107, 108) have used a different approach as an aid in diagnosing hyperthyroidism. First the patient is given an oral dose of a goitrogen (mercaptoimidazole) which, in their opinion, inhibits the accumulation of organically bound iodine in the thyroid. One or two hours later a tracer dose of radioiodine is given and frequent measurements with a Geiger counter are made over the neck for a few hours. In the thyrotoxic patient a greater uptake of radioiodine is observed than in the normal subject. Also discharge of radioiodine from the thyroid under these conditions is more precipitous in the thyrotoxic than in the normal subject after administration of thiocyanate. Astwood and Stanley (109) also evolved an "accumulation gradient" of radioiodine by plotting the radioactivity over the neck against the square root of time after administration of a dose of radioiodine.

These tests have become valuable in helping to establish the diagnosis of hyperthyroidism in doubtful cases. However, it must be kept in mind that renal disease, congestive heart failure (110) and thiocyanate goiter (68) may cause a low renal excretion of radioiodine. Treatment with thiouracil, thyroid, iodine, thiocyanate sometimes, ingestion of gallbladder dye, and

possibly other medications may increase the urinary excretion of radioiodine to very high levels, this phenomenon persisting for varying periods after withdrawal of the medication.

Goiters.—Radioiodine uptake is almost invariably increased both in diffuse toxic goiter and in nodular goiter with hyperthyroidism (111). Hamilton and co-workers (27) stated that diffuse toxic or exophthalmic goiters collect iodine uniformly throughout the gland, but Saylor and Kelsey (112) have found a patchy distribution of radioiodine in such glands (Fig. 10).

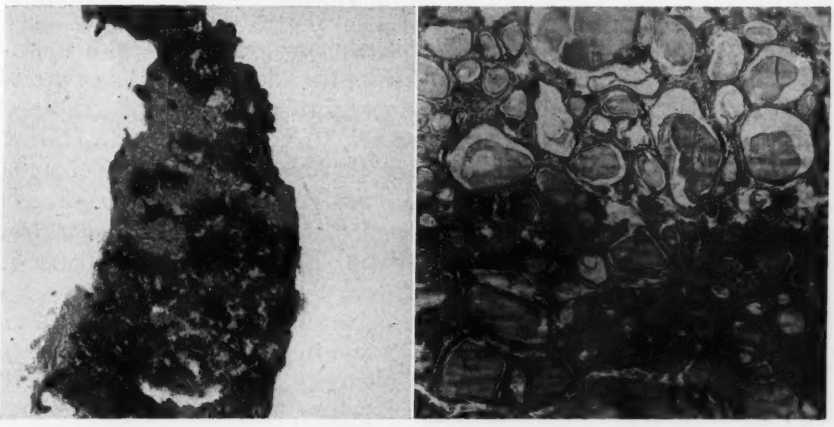


FIG. 10. Autoradiographs of a diffuse toxic or exophthalmic goiter. The goiter was removed nine days after administration of a tracer dose of 300 microcuries of I^{131} and after seven days of treatment with 30 drops of compound solution of iodine daily. There is a patchy distribution of the retained radioiodine throughout the tissue. This irregularity of retention may explain the variability of response of different thyroid glands to approximately the same dose of radioiodine. (Courtesy of Dr. Howard Saylor.)

Nodular goiters are even more difficult to understand, but the question as to whether nodules or adenomas of the thyroid function has been solved so far as uptake of iodine and its conversion to diiodotyrosine and thyroxine are concerned. Saylor and Kelsey (112) found no collection of radioiodine in adenomas within diffuse toxic or exophthalmic goiters while the nonadenomatous tissue showed good collection. Cope, Rawson and McArthur (113) studied patients who had hyperthyroidism and single adenomas of the thyroid. One patient had great uptake of iodine in the adenoma while the nonadenomatous tissue was atrophic and collected iodine poorly. In euthyroid persons who had single adenomas varying degrees of uptake were seen in the adenomas. Some collected more than the uninvolved tissue, others collected less. When an adenoma had high uptake, the uninvolved

tissue had very little uptake and appeared atrophic, so that a hypothetical balance resulted—the normal tissue decreasing its function as the function in the nodule increased, thus maintaining a euthyroid state. When hormone secretion by a single adenoma exceeds the normal need, hyperthyroidism should result. Puppel and co-workers (114–116) reported poor iodine uptake and conversion to organic iodide in adenomas while the para-adenomatous tissue exhibited a good uptake.

Dobyns and co-workers (117, 118) have made autoradiograms of single and multiple nodular goiters and compared I^{131} collection, follicle morphology and mean acinar cell height (M.A.C.H.) of the adenomatous and extra-adenomatous tissue. In cases of adenomatous goiter with hyperthyroidism I^{131} collection and M.A.C.H. of the adenomatous tissue generally exceeded those of the extra-adenomatous tissue. In cases of exophthalmic goiter with adenomas the reverse was true. In general M.A.C.H. of adenomas could be correlated with their I^{131} collection and in one group of cases a continuous spectrum could be formed consisting at the one end of adenomas with flat cells and little collection and at the other of adenomas with tall cells and intense collection. Such "hyperfunctioning" adenomas also occurred in patients without clinical hyperthyroidism. In another group of cases very marked hyperplasia was accompanied by very little collection. This group differed from the first in having a wide distribution of acinar cell heights compared to the narrow distribution of acinar cell heights in the hyperplastic hyperfunctioning adenomas. Dobyns and co-workers expressed the belief that the nonfunctioning group formed a continuous spectrum with papillary adenocarcinoma, the follicles of which showed similar variability of cell size and similar lack of function.

Spencer and co-worker (119) studied multiple adenomatous goiters with and without hyperthyroidism. The adenomas within a single goiter collected variable amounts of radioiodine, some more, others less, than did the nonadenomatous tissue (Fig. 11). Apparently a patient who has nodular goiter will have hyperthyroidism if the total hormone produced by all the tissues with different degrees of function exceeds that required for normal metabolism.

Some diffuse goiters with or without hypothyroidism have been seen with high uptake of radioiodine and high conversion to organic iodide (28, 114–116).

Hypothyroidism.—It is not surprising that patients who have myxedema, having little or no functioning thyroid tissue, excrete about 80 per cent or more of a tracer dose of radioiodine in the urine within seventy-two hours (13, 23, 24) (Fig. 12). Geiger counts over the neck show little or no concentration of radioiodine in the region (18, 101) (Fig. 9). Exceptions may occur in certain goiters with myxedema (28) or in thiocyanate goiter with

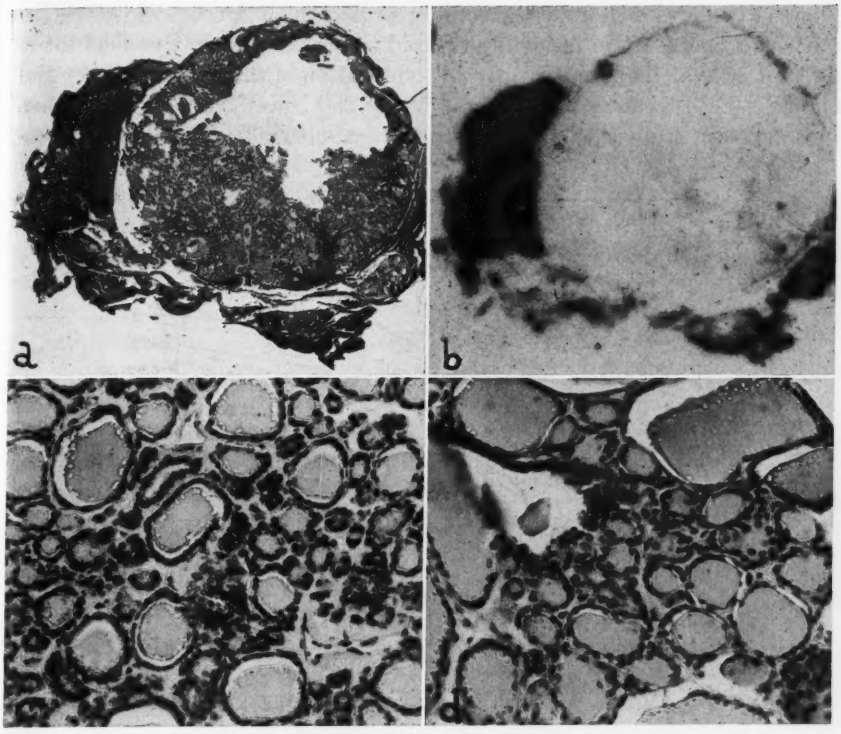


FIG. 11. Autoradiographic study of a multiple adenomatous goiter removed from a patient with hyperthyroidism. *a.* Photomicrograph of the goiter showing several adenomas. *b.* Autoradiograph of the same section. Note variability in uptake of radioiodine, the large central adenoma collecting very little, some smaller peripheral adenomas collecting much, and the nonadenomatous tissue in the lower part of the section collecting a moderate amount. *c.* Photomicrograph of the adenoma at the left of the section. *d.* Photomicrograph of the large central adenoma. Although there is an extreme difference in uptake of radioiodine in the two adenomas, their microscopic appearance is almost identical. (Courtesy of Dr. J. R. Spencer.)

myxedema (72) in which the thyroid is hungry for iodine. Radioiodine uptake by the thyroid is usually diminished in thyroiditis (120) but for some unknown reason this response varies with different patients (111). Elderly normal subjects are said to have a diminished rate of uptake of radioiodine (121).

Other diagnostic tests.—Radioiodine has also been used to determine whether intact tissue or tumor mass is thyroidal in origin (122), whether a complete thyroidectomy has been performed (123) and to discover distant metastatic growths of thyroidal carcinoma (124). Hayden and Corrigan

(125) have developed a Geiger counter probe which can be cold-sterilized for use at operation in localizing thyroid tissue in an operative field made difficult by scar tissue or by retrosternal location of the goiter. Werner and Quimby (126) recently reported the use of 250 tracer doses of radioiodine in diagnostic studies of various thyroidal abnormalities. Seidlin and co-

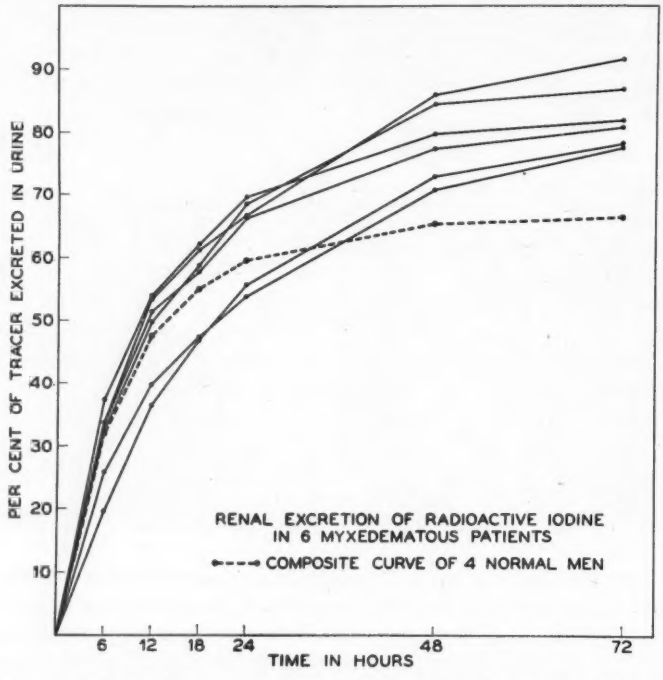


FIG. 12. Cumulative urinary excretion of radioiodine by 6 patients with myxedema. In all cases the per cent of tracer excreted in the urine exceeded that of the composite normal. The excretion curves also did not level off as quickly as did those of the normals. (From Keating, Power, Berkson and Haines (24).)

workers (127) have pointed out the value of tracer studies with radioiodine in cases in which the metabolic rate is high as a result of parkinsonism, anxiety states and heart failure. Skanse and Riggs (97) have found radioiodine tracer studies useful in differentiating spontaneous hyperthyroidism from that induced by ingestion of thyroid.

THERAPEUTIC USES OF RADIOIODINE

Internal irradiation of thyroid tissue with radioiodine affords a means of delivering a much greater amount of radiation than is possible by roent-

gen rays or radium, the dosage of which is limited by radiation damage to tissues other than the thyroid, particularly the skin. Radium or roentgen therapy can be given to a total of 6,000 roentgens (124) while as much as 25,000 equivalent roentgens can be safely administered to the thyroid in a single dose of radioiodine for the treatment of hyperthyroidism (128). Much larger doses have been given in cases of thyroidal cancer without demonstrable serious effect (124, 129). On the other hand, incidental damage to ovaries, kidneys or other organs, an increase in the probability of mutations in offspring (130), or the possibility of a carcinogenic effect of radioiodine have not yet been determined (131). In order to calculate the dosage of radioiodine, the energy and type of radiations, the amount collected per gram of tissue and the approximate weight of the tissue must be known. Several papers have appeared which give information on dosage determinations for radioiodine (40, 79, 129, 132, 133). The most important uses of radioiodine are for treatment of hyperthyroidism and carcinoma of the thyroid but it has been used recently to treat euthyroid cardiac patients by producing myxedema (134).

Hyperthyroidism.—The first thyrotoxic patients to receive radioactive iodine as a therapeutic measure were treated by Hertz and Roberts (102) in 1941. Coincidentally, Hamilton and co-workers (12, 135) gave large doses of I^{131} to dogs and rabbits producing marked destruction of functional tissue in the thyroid with replacement by fibrous tissue. Other tissues, including the recurrent laryngeal nerves, the parathyroids and the trachea, remained normal. With this information three patients who had hyperthyroidism were given smaller doses of I^{131}. Within four to six weeks there was marked clinical improvement and in a few months there was complete remission, with one patient requiring a small second dose.

Subsequent studies (136) have confirmed the foregoing brief reports and some patients now have been observed in remission for several years. Hertz and Roberts (104) treated 29 thyrotoxic patients with a mixture of I^{130}, 90 per cent, and I^{131}, 10 per cent, and noted remission in 20 patients. The small dosage of radioiodine (5 to 28 millicuries) and the subsequent administration of ordinary iodine in these cases makes interpretation of results difficult. Chapman and Evans (105) treated 22 patients having exophthalmic goiter with usually larger doses (14 to 79 millicuries) of the same radioiodine mixture. No other treatment was employed. Fourteen of the patients responded to a single dose while 8 required subsequent dosage. Remissions were complete in 20 patients and partial in 2. In 4 patients myxedema developed. Twenty-one of the patients experienced reduction in size of the thyroid to no goiter or a thyroid that was barely palpable. Fibrosis of the thyroid was seen in the two glands which were biopsied. There was a great diminution in the number of follicles; but the epithelium

remaining still appeared hyperplastic, indicating that radioiodine does not affect the original stimulus causing hyperthyroidism but acts only to destroy the overfunctioning parenchyma. Average time for remission to occur was seven to eight weeks. The blood lipids tended to rise along with fall in metabolic rate while the patient improved clinically. The larger goiters did not respond as quickly as the smaller ones. Toxic reactions seen in 6 cases were much like roentgen ray sickness. Nausea, vomiting, malaise, even slight increase of gland size and fever occurred and lasted two days at most. No subsequent ill effects or leukopenia were noted, and no malignant changes were seen in the two biopsies, one as long as two years after the treatment.

Means (106) reported that Chapman had increased this series of patients to a total of 65 receiving I^{130}. Forty-six of these had become euthyroid, 11 had become hypothyroid and 8 were improved but still thyrotoxic. No recurrences were seen. Means reported that Chapman had also treated 60 patients with I^{131}. Thirty-six had made satisfactory response, with 3 of this group receiving a second dose of I^{131}; 12 were better but still somewhat thyrotoxic six months after treatment; the remainder had not been followed long enough to evaluate.

Soley and Miller (137) treated 33 patients who had diffuse toxic goiter by giving monthly doses of 1,000 to 2,000 microcuries of I^{131} until a therapeutic response occurred. Because of its longer half-life, smaller doses may be given than with I^{130}. Twenty patients responded well in from one and one-half to seven months after the treatment had been started, the average being 3.6 months. As a result of treatment the average estimated weight of the thyroid was reduced from 31 to 13 Gm., the basal metabolic rate from plus 28 per cent to minus 10 per cent, and the serum-protein-bound iodine from 10.7 to 5.7 micrograms per 100 cc. of serum. The average dose of radioiodine in the cases in which treatment was successful was 2,726 microcuries with a range from 800 to 4,500 microcuries. The patients whose treatment was unsuccessful had larger glands, higher metabolic rates and higher serum-protein-bound iodine than did the patients whose treatment was successful. Within twenty-four to seventy-two hours after administration of the dose, often there was definite tenderness of the thyroid gland, increased blood sedimentation rate and serum-protein-bound iodine. At four to ten days there was an increase of thyrotoxicity. Failure of these changes to appear often foretold a poor result. Six of twenty-six patients experienced increase of exophthalmos after treatment.

Haines and co-workers (128) calculated the desired dose of I^{131} before administering it. Capacity of the diseased thyroid to collect radioiodine was determined by a preliminary tracer dose. In the realization that most

of an ingested dose not excreted in the urine within seventy-two hours is collected by the thyroid, this fraction was arbitrarily used as the percentage of an oral dose which the thyroid would collect. Most of the I^{131} collected by the thyroid remains in the gland until its radiations are spent. Weight of the thyroid was estimated in grams after palpation of the patient's neck. Experience proved that in most cases a satisfactory dose of I^{131} delivered to the thyroid was 200 to 250 microcuries per gram of glandular tissue. Dosage was then calculated by the following formula:

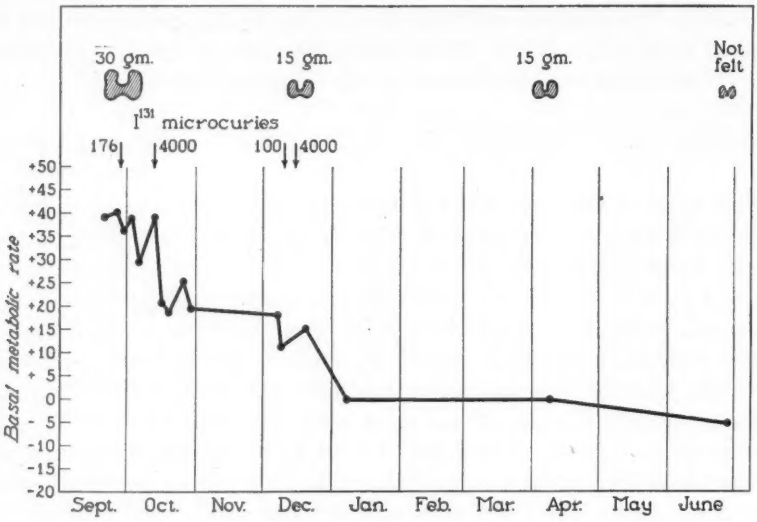
$$\frac{\text{Microcuries per gram (200–250)} \times \text{estimated thyroid weight} \times 100}{\text{Per cent of } I^{131} \text{ tracer collected by thyroid}} = \text{desired dosage in microcuries.}$$

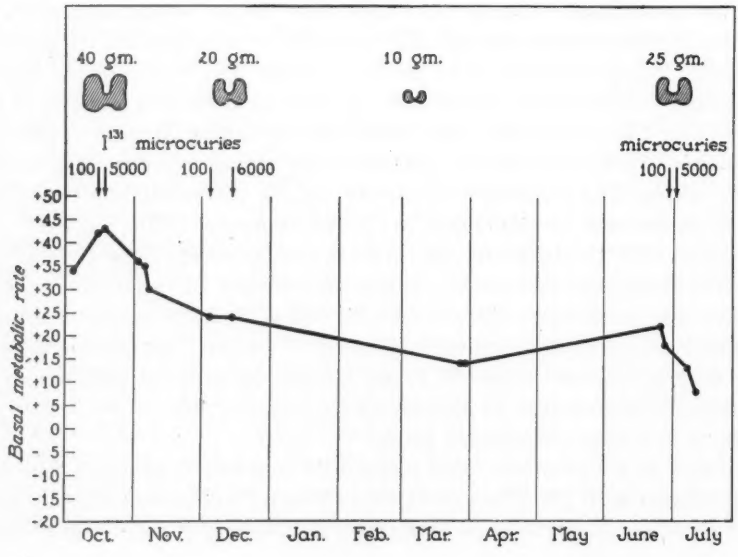
The oral doses varied from 2,600 to 20,000 microcuries. In consideration of possible late effects of radiation, therapeutic radioiodine was given to those patients in whom the risk and difficulties of other methods of treatment appeared to be excessive. These patients included older patients having serious heart disease, multiple recurrences of goiter, vocal cord paralysis, a patient with marked iodine sensitivity making preoperative iodination impossible, and one with coexistent malignant disease outside the thyroid. Of the 40 patients treated, 27 had good, 8 had fair, and 5 had poor results after administration of a single dose. In the 8 cases in which response was fair the hyperthyroidism was later controlled by one or two subsequent doses of radioiodine. In the 5 cases in which the results were poor the patients were given inadequate dosage or the hyperthyroidism was complicated by serious heart disease that may have caused wrong diagnoses. In 8 cases myxedema developed but this was a minor complication considering the critical status of some of the patients. Three had recurrence of hyperthyroidism. One instance of brief roentgen-ray sickness and leukopenia occurred (Fig. 13). A striking observation was the unexplainable variability of response of different thyroid glands to approximately the same dosage of radioiodine. The possibility of spotty uptake of radioiodine by exophthalmic goiter may be significant in this phenomenon (10) (Fig. 10*a*).

Williams (82), in discussing the forms of treatment for hyperthyroidism, listed the following indications for the possible use of radioiodine: 1) inability to get the patient into satisfactory condition for surgical treatment, 2) patient cannot afford surgical treatment, 3) patient fears surgical treatment, 4) multiple recurrences of hyperthyroidism, 5) vocal cord paralysis, 6) extremely large goiter, 7) sensitivity to, refractoriness to, or lack of cooperation in taking antithyroid drugs.

Williams and co-workers (83) treated 98 unselected patients who had thyrotoxicosis with I^{131}. The average dose was 8.5 millicuries given in from one to six doses. Repeat doses were given at intervals of six to eight weeks.

Eighteen patients had not been followed long enough for evaluation; 76 had been euthyroid from three to twelve months and 4 were myxedematous. Temporary exacerbation of thyrotoxicosis as a result of radiation was controlled in some patients by one of the antithyroid drugs before, and with





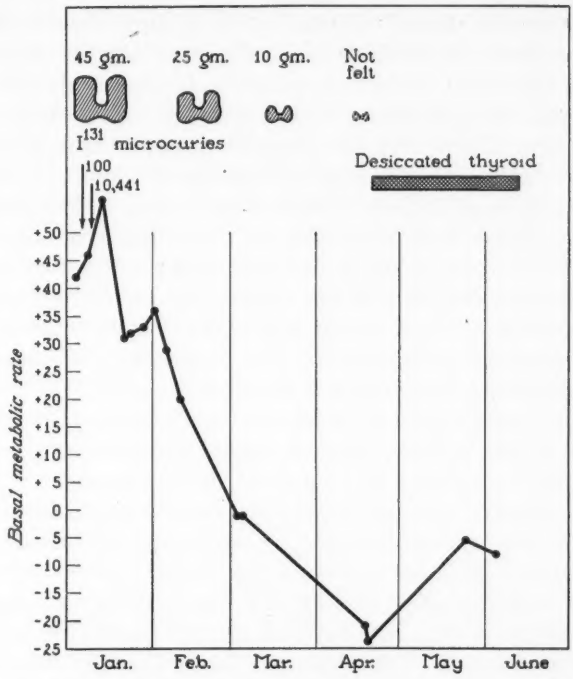


FIG. 13. Sample results in treating exophthalmic goiter with radioiodine. The diagram at the top of each graph represents the estimated size of the thyroid during the course of treatment. The small doses of radioiodine were given for tracer studies, while the larger doses were given for therapeutic purposes. Good result (a), recurrence of hyperthyroidism (b), and occurrence of myxedema (c) are illustrated.

iodide after, the radioiodine was administered. This procedure eventually became routine for all patients. Maximal responses to treatment were noted at six weeks or longer. Soley (120) has stated his conviction "that I^{131} will soon be an accepted satisfactory method of treating a larger proportion of patients with Graves' disease than would be chosen for roentgen therapy and may even replace surgery for the average patient." Haines and co-workers (128) drew no definite conclusions but were interested in its uses for patients who were difficult to control or who were poor surgical risks.

Carcinoma of the thyroid.—Certain types of thyroidal cancer have the capacity of concentrating sufficient quantities of iodine to make internal radiation of them with radioiodine a feasible treatment. Early reports (12, 27) were discouraging but Keston and co-workers (138, 139) soon reported a case in which Geiger counter studies demonstrated the ability of metastatic thyroidal cancer to collect radioiodine. This patient was given an

ineffectual therapeutic dose of radioiodine. At necropsy the only metastatic nodule which collected appreciable radioiodine was found to contain colloid follicles while the other metastatic growths, by histologic examination, were undifferentiated. McArthur and Cope (140) gave radioiodine preoperatively to 18 patients who had discrete thyroid nodules. Six of these nodules turned out to be malignant and collected from none to a fourth as much radioiodine as did adjacent uninvolved tissue. In 3 instances there was detectable collection of radioiodine by metastatic growths.

Five of 12 carcinomas of the thyroid were observed by Rawson and coworkers (118) to collect minimal but measurable amounts of radioiodine. This same degree of function was found to exist in the metastatic growths from 8 of these tumors. Seidlin, Oshry and Yalow (141) demonstrated uptake of radioiodine in the metastatic growths in 8 of 14 thyroidal cancers and treated the positive growths with radioiodine. Soley (120) stated that uptake of radioiodine sufficient for therapeutic purposes was present in the metastatic growths in only 1 of 10 cases of thyroid cancer.

Marinelli, Foote and Hooker (38) studied radioiodine uptake in 19 cases of thyroidal cancer by autoradiography and found 10 neoplasms which took up appreciable amounts of radioiodine; 5 were "benign metastasizing struma" and 5 were follicular adenocarcinoma. Two papillary adenocarcinomas collected only questionable amounts. Considering the incidence of these types of cancer in comparison with the incidence of the types which do not collect radioiodine, about 15 per cent of all thyroidal cancer should collect appreciable amounts of radioiodine. In general only the tumors containing colloid collect radioiodine but certain highly malignant tumors appear to be exceptions to this rule. Not all of the tumors with colloid or follicle formation collected radioiodine. A lack of uniformity of uptake within a cancer was noted. This was not entirely correlated with histologic appearance, for there was no uptake of isotope in some regions the structure of which would ordinarily indicate ability to retain radioiodine. A single biopsy did not always determine whether radioiodine uptake was sufficient for treatment. One case with papillary adenocarcinoma at biopsy of the thyroid showed poor uptake, but Geiger counts showed appreciable uptake in the metastatic growths. Biopsy of the ribs demonstrated a follicular carcinoma.

The impression that there may be a correlation between colloid formation and capacity to collect radioiodine is found in the work of Gorbman (142–146) on the fetal thyroid of rats, which demonstrated that fetal thyroid cannot concentrate iodine until there is differentiation of solid cell cords into follicles and deposition of colloid into the lumina. This transformation occurred at the ninteenth day of fetal life. Chapman (147) has found that human fetal thyroid tissue concentrates radioiodine given to

the mother only after the fourteenth week of pregnancy or after the fetal thyroid has developed to the point of follicle formation and deposition of colloid.

Only 1 case in which thyroidal cancer was treated with radioiodine has been reported in detail (124, 148). The patient had undergone total thyroidectomy twenty years before treatment with radioiodine and functioning metastatic growths and hyperthyroidism developed five years before. Therapeutic doses totaling 110.8 millicuries of I^{130} and 158 millicuries of I^{131} were given orally over a two-year period, nearly 40,000 equivalent roentgens being delivered to the tumors. During two years of observation there was clinical improvement and arrest of the growth of metastatic tissue but the metastatic tissue still retained the ability to collect radioiodine, indicating that the malignant lesion had not been destroyed. There were no serious reactions to the large doses of radioiodine, even though temporary alopecia occurred over a large metastatic area in the skull, and transient leukopenia developed. Leiter and co-workers (148) quoted Hare, who found no response by an alveolar carcinoma of the thyroid after exposure to 6,000 roentgens of x-radiation, but who successfully treated a patient by interstitial implantation of radon with a calculated dose of 20,000 roentgens, a value well beyond the reach of external radiation.

The maximal dose of radioiodine which a human being can tolerate without serious after-effects has not yet been determined. Gorbman (149) gave young mice huge doses of I^{131} (3 to 50 millicuries per kilogram of body weight). The larger doses produced complete destruction of the thyroid within a few days. The smaller doses permitted survival of some thyroidal epithelium but resulted in loss of the parathyroids. Lesions were produced in the tracheal epithelium with all dosages and in the recurrent laryngeal nerve with the larger doses. Possibly the central regions of the thyroid or of a metastatic growth are exposed to more radiation than the peripheral regions (150). Because of spotty uptake and limited penetration of beta particles, it would be well to deliver large enough doses of radioiodine to get therapeutic gamma irradiation (38). Some patients at the Memorial Hospital in New York have received single doses of 250 millicuries of I^{131} without serious toxic effect (129). Uptake of radioiodine by cancers of the thyroid may be increased by removal of the normal thyroid by surgical means or by internal radiation, by giving antithyroid drugs and withdrawing the drug a few days before administration of radioiodine, by injections of thyrotropic hormone (151) or by temporary renal block of radioiodine excretion (38). Rawson (152) noted that occasionally, as one metastatic nodule is destroyed by radioiodine, another begins collecting the isotope and can be treated. There is a hopeful possibility that radioactive organic compounds may be produced which localize in tumor tissue (153).

There is enough tellurium in some doses of radioiodine to produce a physical sign of tellurium ingestion—garlic odor—which may persist for months on the breath of patients treated with large doses of radioiodine for thyroidal cancer (68). Not enough tellurium is ingested to cause toxic symptoms, which would be similar to those of arsenic poisoning.

Addendum.—Since this paper was prepared for publication the following articles have appeared, which should be included in this review:

Nickson (Nickson, James J.: Dosimetric and protective considerations for radioactive iodine, *J. Clin. Endocrinol.* **8:** 707–717 [Sept.] 1948) gives practical abbreviated formulas for calculating therapeutic dosages of, and exposure of personnel to, radioiodine.

Werner and associates (Werner, S. C.; Quimby, Edith H. and Schmidt, Charlotte: The clinical use of radioactive iodine, *Bull. New York Acad. Med.* **24:** 549–560 [Sept.] 1948) reported the treatment with I^{131} of 40 patients who had diffuse toxic goiter. Follow-up studies lasted from four months to more than a year. The dose utilized was determined by measurements over the thyroid with a Geiger counter. There were no failures with a single dose retained by the thyroid of 75 or more microcuries per estimated gram of tissue. Seven of the patients retaining less radioiodine required a second dose. In 4 cases temporary hypothyroidism developed, but this cleared spontaneously.

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The 1949 Meeting of the Association for the Study of Internal Secretions

The Thirty-First Annual Meeting of the Association for the Study of Internal Secretions will be held in the Chalfonte-Haddon Hall, Friday and Saturday, June 3 and 4, 1949, in Atlantic City, New Jersey.

We are informed by the hotel management that reservations will be difficult to secure on short notice; therefore, members are urged to make reservations at once with Chalfonte-Haddon Hall, giving time of arrival and length of stay in Atlantic City.

The scientific sessions will be held in the Viking Room, as formerly, and registration will be on the same floor. The annual dinner will be held in the Rutland Room, Friday, June 3, at 7 p.m., preceded by cocktails in the same room.

Those wishing to present papers, which will be limited to ten minutes, should send the title and four copies of an abstract of not more than 200 words, to Dr. J. S. L. Browne, Royal Victoria Hospital, Montreal 2, Canada, not later than March 1, 1949. It is imperative that the abstracts be informative and complete, with results and conclusions, in order that they may be of value for reference and suitable for printing in the program.

Nominations for the Squibb and Ciba Awards and the Ayerst, McKenna and Harrison Fellowship should be filed on special forms with the Secretary of the Association, not later than March 15, 1949, according to specifications given in the section on Awards.

The 1949 Annual Meeting of the American Diabetes Association

CHALFONTE-HADDON HALL,
ATLANTIC CITY, N. J.

SATURDAY AFTERNOON, JUNE 4;
SUNDAY MORNING AND AFTERNOON, JUNE 5.

BANQUET, SATURDAY NIGHT.

Please send reservations for the banquet now to this office. Wives of members are welcome. Dinner subscription—$6.00—*Payable when you register* at the meeting.

The 1949 Meeting of the American Goiter Association

The next annual meeting of the American Goiter Association will be held at the Loraine Hotel in Madison, Wisconsin, May 26, 27 and 28, 1949.

All members of the Association are urged to make their hotel reservations as early as possible. Those who would prefer a resort hotel will find the new Edgewater very beautiful. It is half a mile from the Loraine on the shores of Lake Mendota.

The officers of the Society are as follows:

President	—Arnold S. Jackson, Madison, Wisconsin
President Elect	—Samuel F. Haines, Rochester, Minnesota
Vice President	—Willard O. Thompson, Chicago, Illinois
Corresponding Secretary	—T. C. Davison, Atlanta, Georgia
Recording Secretary	—Geo. C. Shivers, Colorado Springs, Colorado
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J. H. Means, Boston, Massachusetts
Elmer Bartels, Boston, Massachusetts
Allen Graham, Pittsburgh, Pennsylvania
H. P. Sloan, Bloomington, Illinois
D. U. McGregor, Hamilton, Ontario, Canada

Dr. George Crile, Jr. of Cleveland is Chairman of the Program Committee.

Announcement of Jefferson Medical College and Hospital Fellowship

A Fellowship in obstetric and gynecologic endocrinology will be available at the Jefferson Medical College and Hospital, Philadelphia, on or about May 1, 1949, under the direction of Dr. A. E. Rakoff, Assistant Professor of Obstetrics and Gynecology, and Endocrinologist to the Department of Clinical Laboratories.

The Fellowship is available to Doctors of Medicine who have had at least one year or its equivalent of postgraduate training in obstetrics and gynecology. Applicants for the Fellowship should communicate at once with Dr. Lewis C. Scheffey, Professor of Obstetrics and Gynecology, Head of Department, and Director of Division of Gynecology, Jefferson Medical College and Hospital, Philadelphia 7, Pa.